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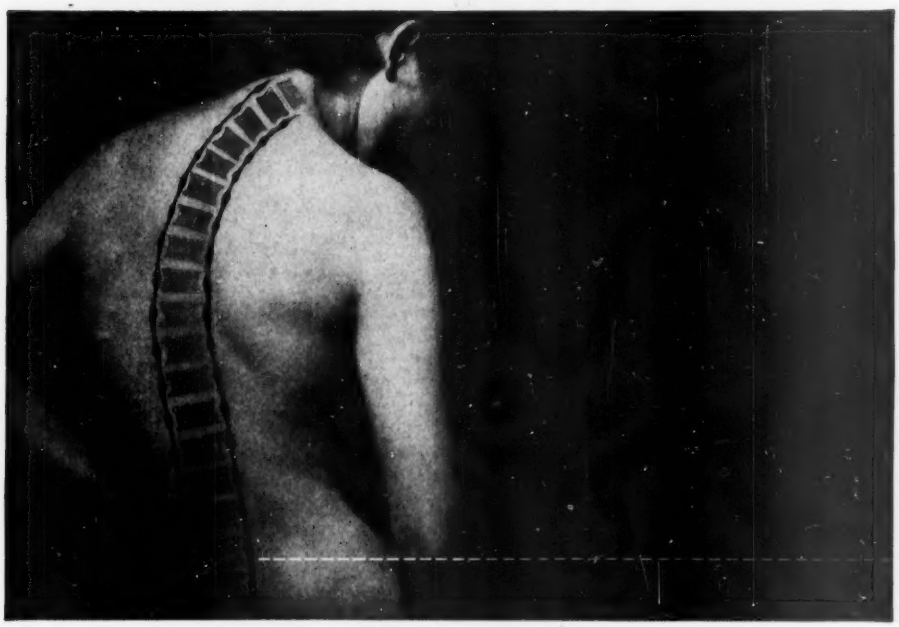

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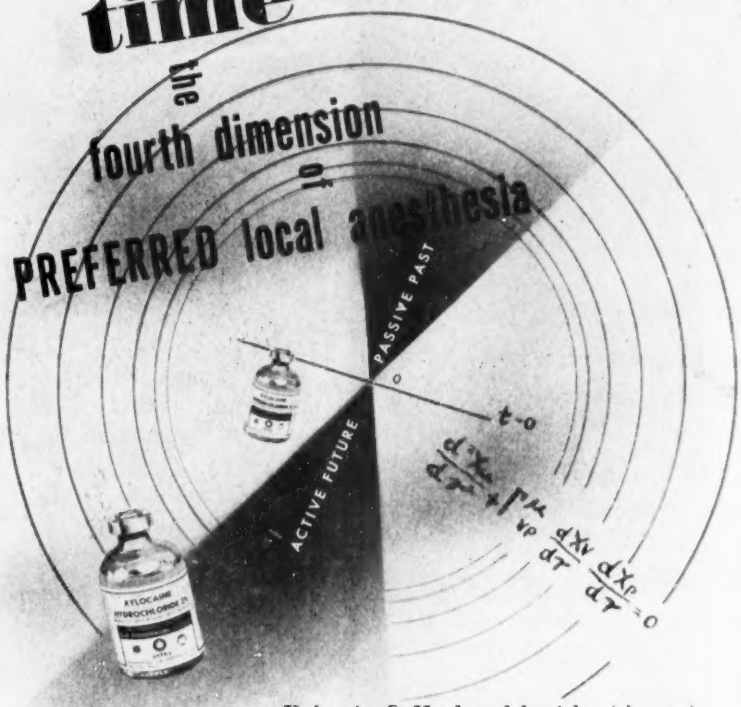

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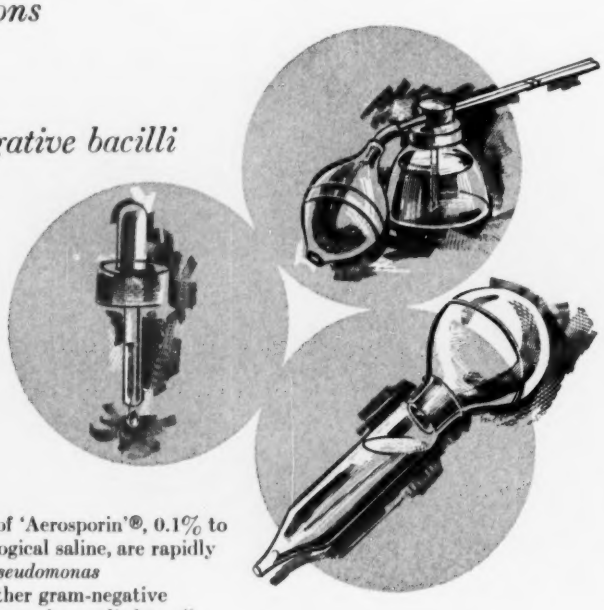

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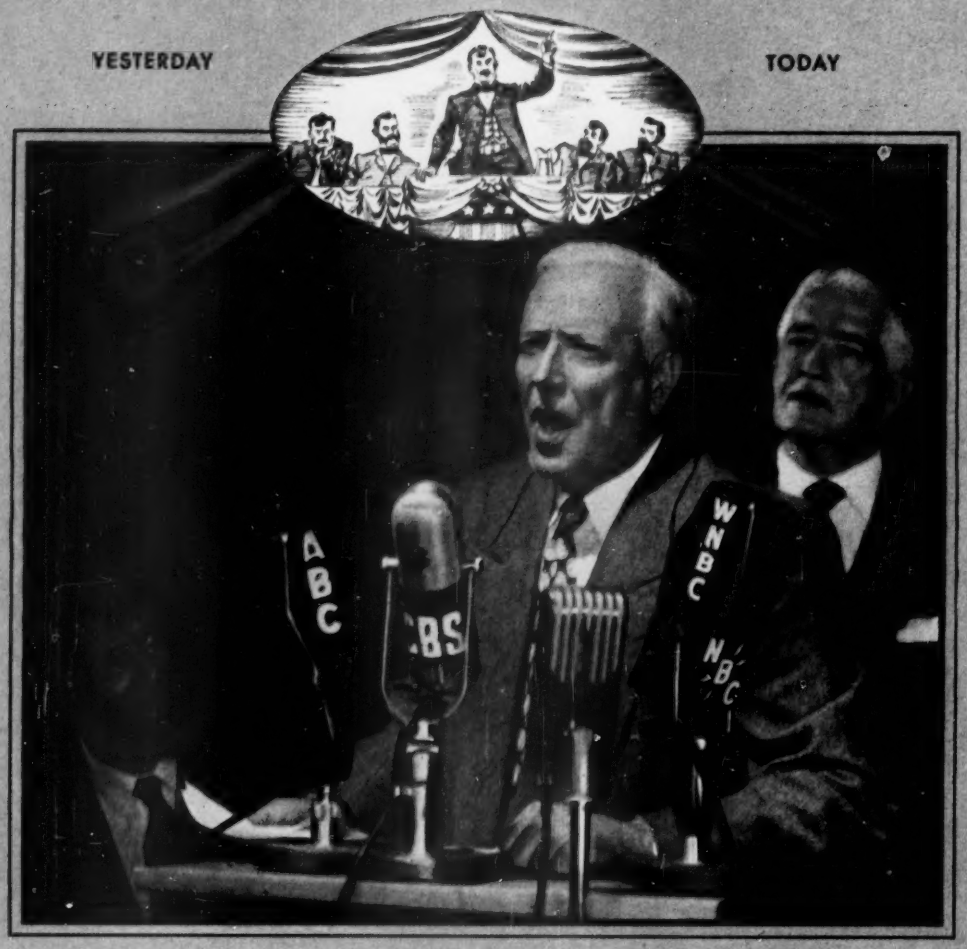

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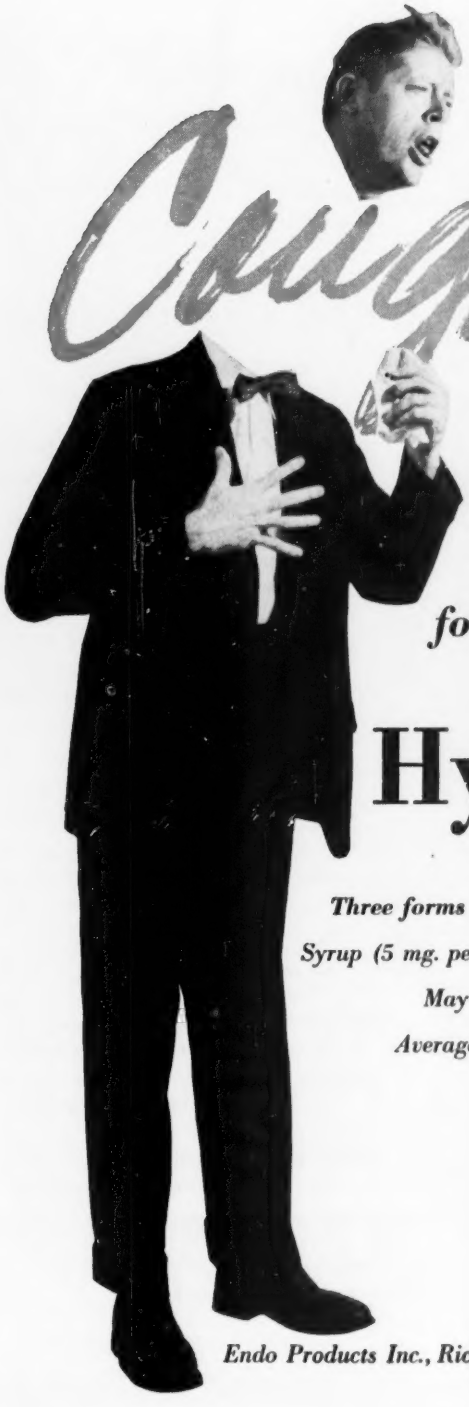

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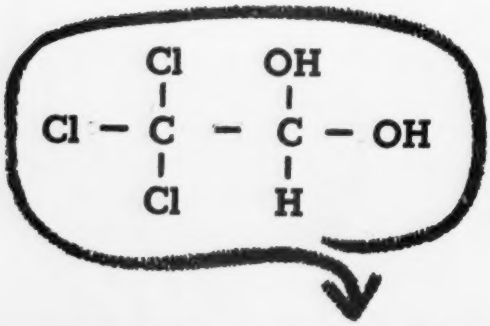

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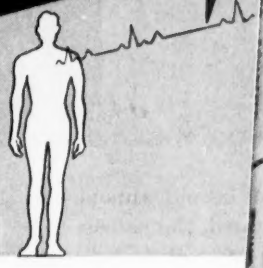

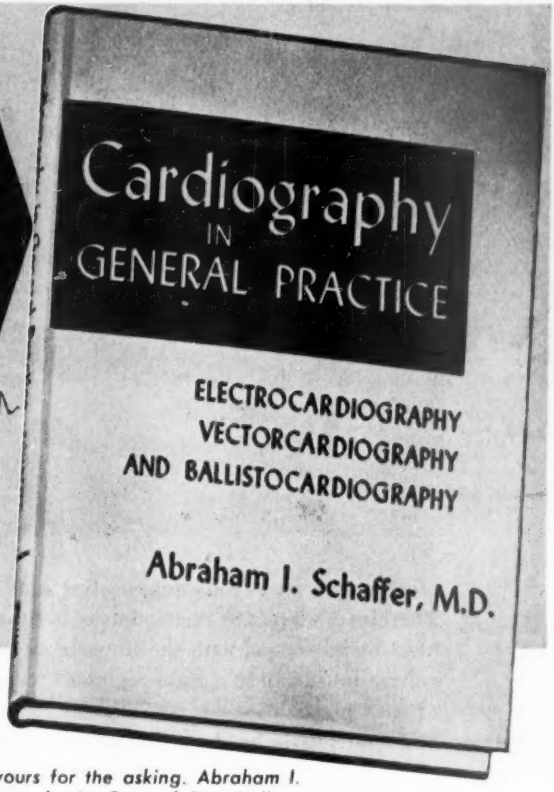

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Journal of Medicine

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Volume 248 JANUARY 15, 1953 Number 3

PULMONARY FUNCTION AFTER SEGMENTAL PULMONARY RESECTION FOR BRONCHIECTASIS*

BENJAMIN E. ETSTEN, M.D.,† RICHARD H. OVERHOLT, M.D.,‡ JAMES H. WALKER, M.D.,§ AND ROBERT N. REYNOLDS, M.D.¶

BOSTON

SEGMENTAL pulmonary resection for bronchiectasis is based on the concept that it is most advantageous to conserve all healthy tissue and limit resection to the specific pulmonary segments destroyed by the disease.

Bronchiectasis may affect any of the eighteen segments of the two lungs. In the majority of cases the disease does not involve the entire group of segments that constitutes a pulmonary lobe. Frequently, the disease is bilateral. It has been noted that the superior segment of both lower lobes and the two top segments of the left upper and right upper lobes are not often involved. When bronchiectasis occurs in a young patient the abnormal pulmonary segments contract, and the uninvolved segments hypertrophy as a compensatory mechanism that increases size and function. If bronchiectasis develops after adulthood, the remaining uninvolved segments enlarge by compensatory emphysema,

TABLE 1. *Ventilation Studies (Maximum Breathing Capacity and Walking Ventilation) after Segmental Resection.*

PATIENT	AGE	LOBES RESECTED	NO. OF REMAINING SEGMENTS	MAXIMUM BREATHING CAPACITY		WALKING VENTILATION	WALKING INDEX*	REMARKS
				DETERMINED liters/min.	PREDICTED %	liters/min.		
	yr.							
Unilateral resection:								
F. M.	40	Left basal and lingula	13	56.0	69	11.9	0.17	Contralateral bronchiectasis
M. M.	23	Right middle lobe	16	145.0	92	21.0	0.15	Congenital absence of fissures; segmental technic used.
E. C.	30	Left lower lobe and lingula	12	68.0	98	17.1	0.25	
L. R.	47	Lingula and superior segment of left lower lobe	15	66.0	88	13.9	0.21	
N. F.	53	Posterior and lateral basal left lower lobe	16	88.0	74	22.5	0.25	
A. D.	29	Left lower lobe and lingula and anterior of left upper lobe	11	84.0	67	18.0	0.21	Left temporary phrenic-nerve crush
Bilateral resection:								
G. Z.	29	Left and right basal segments	11	104.0	83	16.9	0.16	
A. R.	27	Right middle lobe, right lower lobe and left basal segment	8	80.0	57	25.0	0.31	
F. O.	43	Left lower lobe and lingula, right middle lobe and right basal segment	6	67.0	55	13.8	0.21	
H. K.	29	Left basal segment and lingula, right basal segment and right middle lobe	7	55.0	58	21.5	0.39	Congenital absence of fissures on left
R. H.	28	Left lower lobe and lingula and right middle lobe	10	75.2	91	19.7	0.26	
C. F.	34	Left lower lobe and lingula, right middle lobe and anterior of right upper lobe	9	73.0	81	12.8	0.17	
H. M.	33	Right middle lobe, lateral basal right lower lobe, left basal segment and inferior lingula	11	56.8	78	17.0	0.30	
R. D.	39	Left lower lobe and lingula, right basal segment, inferior subsegment of anterior segment of right upper lobe and right middle lobe	5½	39.0	53	12.2	0.31	

*WV
MBC

*Presented at the semiannual meeting of the New England Surgical Society, Boston, March 26, 1952.
From the Pratt Diagnostic Clinic, New England Center Hospital, and Tufts College Medical School.

†Professor of surgery (anesthesia), Tufts College Medical School; director, Department of Anesthesiology and Pulmonary Function Laboratory, Pratt Diagnostic Clinic and New England Center Hospital.

‡Clinical professor of thoracic surgery, Tufts College Medical School; thoracic surgeon, New England Deaconess Hospital.

§Teaching fellow in thoracic surgery, Tufts College Medical School; thoracic surgeon, New England Deaconess Hospital.

¶Instructor in surgery (anesthesia), Tufts College Medical School; assistant in anesthesia, Pratt Diagnostic Clinic and New England Center Hospital.

and the affected lung tissue decreases in size and function. Excision of the diseased segments usually results in little increase in size in the remaining tissue, because anatomic adjustments have already been made. Theoretically, therefore, segmental resection for bronchiectasis is a conservative procedure since normal functioning tissue is spared, whereas in lobectomy, one or more normal segments are usually forfeited with removal of the diseased segments of the affected lobe. Segmentectomy is the more difficult procedure, however, and requires more diligent care during the postoperative course.

Table 2. *Timed Vital Capacity, Air Velocity Index and Ventilation Equivalent after Segmental Resection.*

Patient	No. of Remaining Segments	Timed Vital Capacity			Air Velocity Index	Ventilation Equivalent*
		at 1 sec.	at 2 sec.	at 3 sec.		
		%	%	%		liters/min.
Unilateral resection:						
F. M.	13	80	88	94	0.84	2.6
M. M.	16	90	95	98	0.93	1.86
E. C.	12	75	94	100	0.98	3.2
L. R.	15	78	92	96	0.98	2.8
N. F.	16	82	90	98	0.93	3.2
A. D.	11	80	90	95	0.90	2.8
Bilateral resection:						
G. Z.	11	76	94	98	1.10	2.4
A. R.	8	70	85	90	1.0	2.4
F. O.	6	—	—	—	0.59	2.3
H. K.	7	78	85	100	0.84	2.5
R. H.	10	80	85	95	1.79	3.0
C. F.	9	—	—	—	1.16	3.1
H. M.	11	76	91	95	0.94	4.4
R. D.	5½	90	95	100	1.70	1.9

Can individual segments be made to re-expand and function physiologically? The purpose of this paper is to present the results of postoperative pulmonary-function studies on patients with bilateral and unilateral segmental resection for bronchiectasis. The data presented are concerned with the functional effect of hyperinflation and the degree of pulmonary function in patients after extensive unilateral or bilateral segmental resections.

Methods

Fourteen unselected patients who had had either unilateral or bilateral segmental resections from one to seven years before this study were admitted to the New England Center Hospital. Of this group, 2 patients — namely, M. M. and H. K. — had congenital absence of fissures between lobes. In patient H. K. the fissure of the left lung was absent. In patient M. M. the major and minor fissures of the right lung were absent. Because of this congenital anomaly, the right middle lobe was removed by the technic of segmentectomy. The following pulmonary-function studies as related to ventilation and resting arterial blood gases were obtained during the fasting state.

Ventilation Studies

With the patient in the standing position, total vital capacity was recorded on a modified Benedict–Roth spirometer. The timed vital capacity (VC) was measured with a vital-capacity spirometer.[1] Oxygen consumption, tidal volume, respiratory minute volume (RMV), inspiratory capacity and expiratory reserves were read on a balanced spirometer with soda lime in the circuit. The maximum breathing capacity (MBC) was obtained with a Hans–Rudolph high-velocity respiratory valve and a Douglas bag.[2] The gas was collected for thirty seconds, measured by a Tissot spirometer and reported in liters per minute at 37°C. wet; the best of three efforts was recorded. The walking ventilation test consisted of a level walk for three minutes at the rate of 180 feet per minute.[3] The expired air was collected in a Douglas bag; the volume was measured like that of the MBC and recorded in

Table 3. *Differential Bronchospirometric Studies after Segmental Resection.*

Patient	Total No. of Segments	Right Lung				Left Lung			
		No. of Remaining Segments	Oxygen Consumption	Ventilation	Vital Capacity	No. of Remaining Segments	Oxygen Consumption	Ventilation	Vital Capacity
			%	%	%		%	%	%
Unilateral resection:									
F. M.	13	10	59.6	58.5	63.9	3	40.4	51.5	36.1
M. M.	16	8	45.8	52.7	49.9	8	54.2	47.3	50.1
E. C.	12	10	81.2	73.8	77.3	2	18.8	26.2	32.7
L. R.	15	10	70.0	58.1	66.2	5	30.0	41.9	33.8
N. F.	16	10	63.4	59.1	68.8	6	36.6	40.9	31.2
A. D.	11	10	77.4	72.0	80.0	1	22.6	28.0	20.0
Bilateral resection:									
G. Z.	11	6	47.0	54.0	55.0	5	53.0	46.0	45.0
A. R.	8	3	39.3	38.0	45.7	5	60.7	62.0	54.3
F. O.	6	4	59.5	66.4	62.9	2	40.5	33.6	37.1
H. K.	7	4	58.2	67.3	60.0	3	41.8	32.7	40.0
R. H.	10	8	66.7	71.0	72.0	2	33.3	29.0	28.0
C. F.	9	7	76.5	47.6	62.0	2	23.5	52.4	38.0
H. M.	11	7	58.0	48.0	51.0	4	42.0	52.0	49.0
R. D.	5½	3½	—	—	—	2	—	—	—

liters per minute at 37°C. wet. The walking index[3] was calculated from the equation:

$\frac{\text{Walking ventilation}}{\text{MBC}} \times 100$. The predicted MBC and VC were calculated according to Cournand's regression formulas.[4] The air velocity (AVI) index[5] was calculated from: $\frac{\text{per cent of predicted MBC}}{\text{per cent of predicted VC}}$. The ventilation equivalent for oxygen was calculated from the equation: $\frac{\text{minute ventilation in liters}}{\text{minute oxygen uptake in cc.}}$. This is reported as the number of liters ventilated for 100 cc. of oxygen removed.

Differential Bronchospirometry

The patients were sedated with 75 mg. of pentobarbital and 0.6 mg. of scopolamine thirty minutes before the start of the procedure. Laryngotracheobronchial anesthesia was obtained with 4 per cent cocaine, and a Carlens double-lumen catheter was inserted under fluoroscopic guidance.[6] Oxygen consumption, tidal exchange, respiratory minute volume, inspiratory reserve, expiratory capacity and vital capacity were recorded on a twin spirometer.

Total Lung Volume

The patient was allowed to rest in the supine position for thirty minutes before measurement of the functional residual capacity, which was done with the Darling[7] open circuit, slightly modified. After the first determination, the inspiratory capacity, residual capacity and vital capacity were recorded on a Warren–Collins respirometer. After a two-hour interval of rest, measurement of the functional residual capacity was repeated. The following determinations were obtained: functional residual capacity, residual volume, total capacity and alveolar nitrogen content after seven minutes of oxygen breathing. Prediction of the total lung capacity was made according to the formulas used by Baldwin et al.[4]

Arterial Blood Studies

Arterial oxygen content, capacity and carbon dioxide determinations were made on 1-cc. samples of whole blood by the method of Van Slyke and Neill.[8] The arterial blood for pH was determined by a Beckman model G glass electrode. The pH was corrected for a temperature of 38°C.[9] The carbon dioxide tension was calculated from the carbon dioxide content in volumes per cent and the pH value by means of the nomogram of Peters and Van Slyke.[10] Total carbon dioxide values in millimols per liter were read from the chart of Peters and Van Slyke.[11]

TABLE 4. *Lung Volumes after Segmental Resection.*

PATIENT	TIDAL VOLUME	RESPIRATORY MINUTE VOLUME	OXYGEN UPTAKE	VITAL CAPACITY	MAXIMUM INSPIRATION	MAXIMUM EXPIRATORY RESERVE	FUNCTIONAL RESIDUAL CAPACITY	RESIDUAL VOLUME	TOTAL LUNG CAPACITY	RELATION OF RESIDUAL VOLUME TO TOTAL LUNG CAPACITY	INTRAPULMONARY MIXING INDEX
	cc.	*liters/min.*	*cc./min.*	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	*%*	*%*
Unilateral resection:											
F. M.	746	5.2	208	2274	1156	888	—	—	—	—	—
M. M.	723	8.3	448	4438	2932	1527	1645	118	4556	3	0.77
E. C.	376	8.4	325	1799	1657	326	917	591	2390	25	0.55
L. R.	806	8.8	314	2120	1640	393	1329	918	3058	30	1.00
N. F.	668	13.6	453	3076	2307	789	1843	1054	4130	25	1.13
A. D.	748	10.4	369	2932	2265	689	1914	1044	3976	26	1.20
Bilateral resection:											
G. Z.	607	7.6	326	3107	1893	1174	2215	1041	4148	25	0.67
A. R.	397	7.9	334	2883	1722	1019	2759	1740	4623	38	2.46
F. O.	630	6.3	270	3760	2290	1050	—	2470	5900	42	—
H. K.	728	8.7	304	2023	1376	749	1584	835	2858	29	1.03
R. H.	346	7.6	256	1496	916	631	1150	519	2015	26	1.37
C. F.	445	5.3	179	2139	1116	883	—	—	—	—	—
H. M.	446	7.5	248	2393	1521	1014	1763	749	3142	24	1.15
R. D.	348	5.2	241	1267	879	552	1322	666	1933	35	1.11

RESULTS

Total results of the study are summarized in Tables 1 to 5.

In the group of patients with unilateral and bilateral segmental resection, comparison of the remaining number of conserved segments with percentage predicted maximum breathing capacity showed a close agreement (on a percentage basis). The walking index was within normal limits in all cases (Table 1). This ratio correlates the degree of clinical dyspnea associated with moderate exercise.[3]

The timed vital capacity, air velocity index and ventilation equivalent were also within normal limits. These results probably indicate that there is no obstructive emphysema and impairment of air flow during respiration (Table 2).

The findings of differential bronchospirometric studies are listed in Table 3.

These studies show that the percentage of total oxygen consumption increased as the number of

conserved segments increased. The residual volume, in relation to the total lung capacity, and the index of intrapulmonary mixing were within normal limits

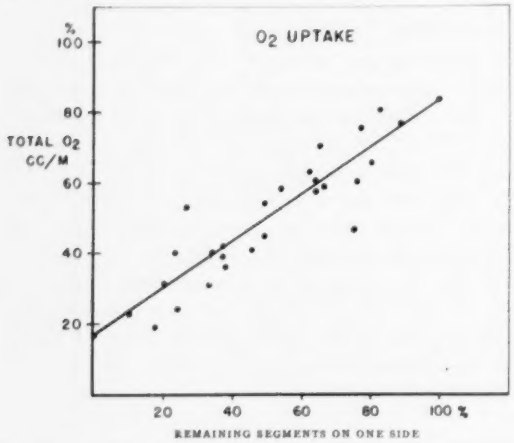

FIGURE 1. *Differential Bronchospirometric Studies (Oxygen Uptake) after Segmental Resection.*

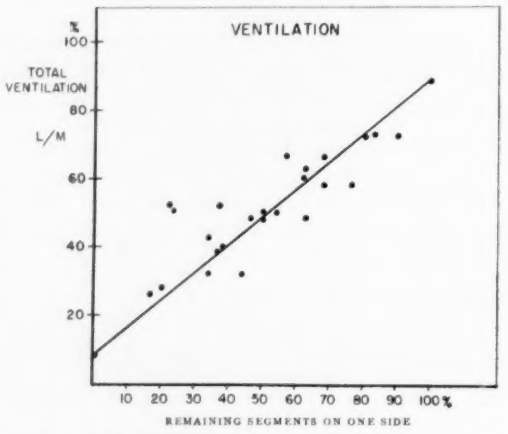

FIGURE 2. *Pulmonary Ventilation in Relation to Number of Remaining Segments.*

except in 1 patient. Total lung volumes were obtained in 11 of the 14 patients (Table 4).

In each case the remaining pulmonary segment or segments contributed to oxygen consumption and ventilation. Patient A.D. demonstrates the comparative degree of ventilation and oxygen consumption on a remaining hypertrophied segment after excision of seven segments from the left lung. This one segment contributed 20 per cent of the total oxygen consumption, and its overdistention did not impair total intrapulmonary mixing.

A comparison of the oxygen consumption and ventilation of the normal lung with that of the operative side gave the following results: the greater the number of conserved segments, the greater the oxy-

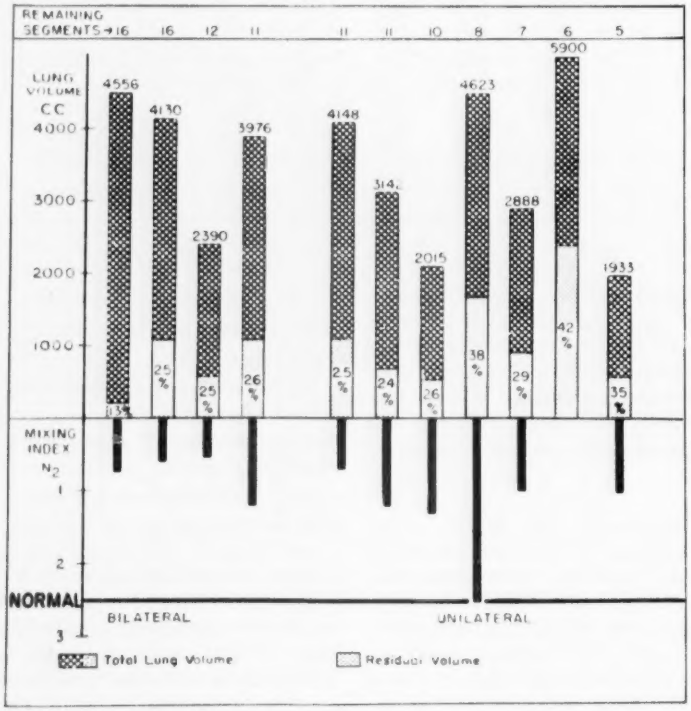

FIGURE 3. *Lung Volume and Mixing Index after Segmental Resection.*

gen consumption and ventilation; and one or two remaining segments contributed significantly to the total pulmonary function.

In the group of patients who had had bilateral-segment operations, the oxygen consumption and did not impair intrapulmonary mixing. Four of the 11 patients had relative increases in residual volumes. One patient in this group had an elevated mixing index and relative increase in residual air; this patient had clinical evidence of emphysema

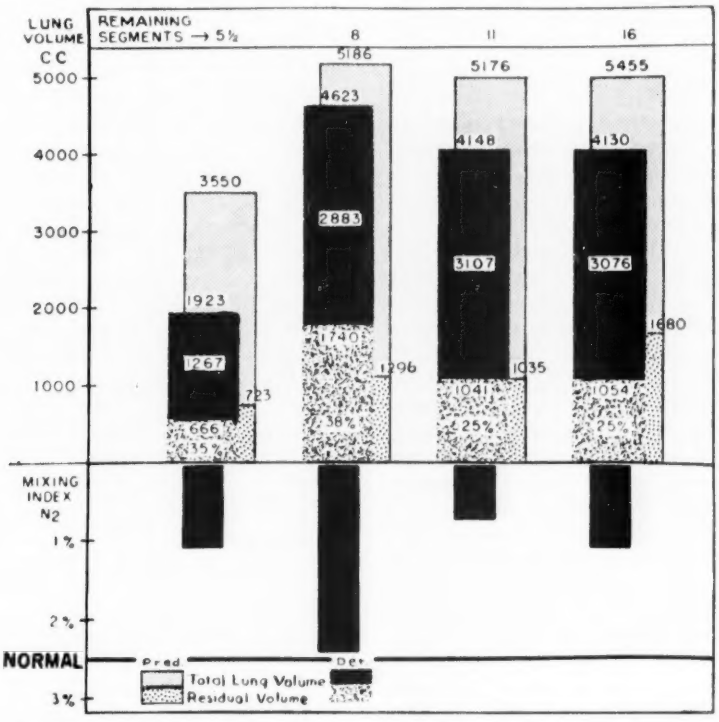

FIGURE 4. *Total Lung Volume Determined and Predicted for Eighteen Segments.*

ventilation figures paralleled the percentage number of remaining segments.

Figures 1 and 2 show the function of pulmonary segments in relation to oxygen consumption and ventilation. In some patients, with only 20 per cent of the total number of segments on one side, these contributed from 20 to 40 per cent of the total oxygen consumption (Fig. 1).

As the percentage of the total number of segments on one side increased, the percentage of oxygen consumption increased. The percentage of total ventilation also paralleled the number of remaining segments, except in patients who had a small number of remaining segments. In these patients pulmonary ventilation increased out of proportion to the number of segments (Fig. 2).

The relations of the residual air to total lung volume and mixing index are shown in Figure 3.

The question whether or not the hyperinflation that followed extensive segmentectomy impaired intrapulmonary air mixing or contributed to emphysema needed clarification. This problem was investigated, and it was found that in all but 1 patient hyperinflation after segmental resection and dyspnea on mild exercise. Four representative cases are shown in Figure 4.

TABLE 5. *Resting Arterial Blood Gases after Segmental Resection.*

PATIENT	OXYGEN SATURATION	CORRECTED pH	CARBON DIOXIDE TENSION*	TOTAL CARBON DIOXIDE
	%	*at 37°C.*	*mm. hg.*	*millimols/liter*
Unilateral resection:				
F. M.	—	—	—	—
M. M.	95.0	7.53	33.0	27.0
E. C.	94.6	7.45	33.5	23.2
L. R.	97.0	7.25	48.8	21.3
N. F.	94.0	7.38	49.0	23.4
A. D.	95.0	7.45	39.0	26.7
Bilateral resection:				
G. Z.	96.0	7.41	40.5	25.4
A. R.	97.0	7.41	30.0	19.5
F. O.	—	—	—	—
H. K.	95.0	7.53	33.0	27.0
R. H.	96.0	7.36	45.5	25.5
C. F.	—	—	—	—
H. M.	92.0	7.55	29.0	25.0
R. D.	—	—	—	—

*Calculated from carbon dioxide content (vol. per cent) and pH value by means of nomogram of Peters and Van Slyke.[16]

One patient had a total of five and a half remaining segments after bilateral operations. The pulmonary tissue became hyperinflated and filled the

thoracic cage. The increase in residual volume was only 10 per cent above that of normal, and the alveolar nitrogen value (an index of intrapulmonary mixing) after seven minutes of oxygen breathing was within normal limits.

The resting arterial blood oxygen saturation and carbon dioxide tension were within normal limits in all the patients studied (Table 5).

Discussion

Postoperative pulmonary-function studies indicated that both unilateral and bilateral segmental pulmonary resections conserved the integrity of a large number of factors related to ventilation. The more the number of conserved healthy segments, the more the MBC approached the predicted value for normal. The reduction in the determined MBC in some patients did not correlate with their excellent clinical respiratory reserves. It appears that the reduction in MBC must be large to be clinically significant. This is in agreement with the finding of Comroe.[12] Differential bronchospirometric studies showed that each conserved segment contributed to oxygen consumption and ventilation. True emphysema was demonstrated in 1 out of 11 patients; the increased residual volumes in the remaining patients were consistent with overdistention rather than true emphysema.

It is recognized that postoperative atelectasis, pleuritis and pneumonia impair respiratory function. The important factors in preservation of normal function in segments remaining after resection are careful excision of the diseased pulmonary segments, a minimum of operative manipulation of the healthy segments and minimal postoperative respiratory complications.

Conclusion

Pulmonary-function studies after unilateral and bilateral segmental resection for bronchiectasis demonstrate that a healthy segment, conserved, contributes to efficient function.

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TOTAL ADRENALECTOMY FOR REACTIVATED CARCINOMA OF THE PROSTATE*

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An effective new approach to the treatment of neoplastic disease was provided by Huggins and Hodges[1] when they demonstrated the control of cancer of the prostate by orchiectomy and the administration of estrogens. Simultaneously, Munger[2] achieved a similar though less effective result by radiation of the testes. During the last ten years extensive confirmation of the value of these contributions has been obtained. However, subsequent reactivation of cancer of the prostate after inhibition by hormonal therapy has been a consistent and challenging aspect of the course of the disease. Following the logical assumption that androgens are an activating factor in the growth of prostatic cancer, Huggins and Scott[3] attempted the further elimination of androgens by total adrenalectomy. Some clinical improvement was observed after this procedure during several months' survival, but this was limited because of inadequate available substitution therapy at that time (1945). A similar effort was made by Cox[4] in 1947. Recently, the availability of cortisone has made survival and an active existence possible in the absence of the adrenal glands.[5] Further investigation of the effects of total adrenalectomy upon reactivated cancer has already been reported by Huggins,[6] Scott,[7] Baker,[8] Leadbetter,[9] McLaughlin[10] and others.[11]

An apparent increase of adrenocortical activity occurs, perhaps as a compensatory phenomenon, after orchiectomy. There is an initial fall in urinary 17-ketosteroid excretion, which soon rises, according to the observations of Huggins and Hodges.[1] There is some evidence — obtained by repeated measurements of 17-ketosteroid excretion — that estrogens

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may inhibit this enhanced adrenocortical activity after orchiectomy and also that estrogens simultaneously delay the reactivation of the prostatic cancer; we have found an average fall in 17-ketosteroid excretion from 13 mg. to 7 to 9 mg. per twenty-four hours. This level has been maintained fairly consistently, with only transitory rises in response to stress in most cases, for as long as twenty-four months with continuous estrogen administration. The attempt has been made to ascertain a rise in 17-ketosteroid excretion as a signal of increased adrenal activity and consequent reactivation of cancer because of escape from hormonal control. Such a correlation of increased 17-ketosteroid excretion and coincident reactivation of prostatic cancer would be an important observation but has not yet been a consistent finding in our patients. More specific and accurate methods of measuring adrenocortical activity will be employed to discover if such a correlation exists.

Before a study of total adrenalectomy for reactivated cancer of the prostate was undertaken, it seemed advisable to determine if benefit would be derived from the administration of cortisone. This effort was primarily based on the already demonstrated inhibitory effect of cortisone on the adrenal cortex and also on its antianabolic effect on protein metabolism in contradistinction to the action of testosterone. Nine patients were treated with cortisone in a dosage of 25 to 37 mg. a day for periods of one to three months after initial doses of 100 mg. for several days. All but 1 patient had an improved sense of well-being and some relief of pain. There was no objective evidence of regression of neoplastic tissue. In all patients 17-ketosteroid excretion diminished on this dose of oral cortisone, indicating a degree of adrenocortical inhibition. The usual fall was from approximately 10 mg. to 6 mg. in twenty-four hours on this regimen. One patient (Case 7), before total adrenalectomy, was recently treated for three weeks with 100 mg. of cortisone by mouth per day. Relief of pain from osseous metastases was accomplished after five days, and in ten days the serum acid phosphatase of 330 Gutman units per 100 cc. had decreased to 5.8 Gutman units. It must be recognized that this improvement is not entirely from the effect of cortisone on the adrenal cortex, since an observed clinical change and measured improvement in serum acid phosphatase occurred after administration of large doses of compounds E and F in 1 patient who had had a poor response to total adrenalectomy. From these results it is concluded that further efforts at pharmacologic inhibition of the adrenal cortex should be investigated. Currently, a comparative study of the effect of compounds E, B, and F on adrenal function and on reactivated cancer is in progress.

It is the purpose of this communication to describe the studies and early clinical course of 7 patients subjected to total adrenalectomy for cancer of the prostate. All the patients selected were suffering from reactivated carcinoma with recurrent regional and metastatic disease in spite of previous orchiectomy and continuous estrogen therapy for six months to five years. Four had vesical obstruction with urinary retention (2 complete and 2 partial). One had complete obstruction of the right ureter as well. Obstruction of the rectum in 2 patients by cancer of the prostate had required colostomy. Six had extensive osseous metastases, with unremitting pain, demanding constant sedation and narcosis. In 5 of these the pain was completely relieved soon after total adrenalectomy. The improvement persisted after the cortisone dosage had been reduced to maintenance levels. Improvement of appetite concomitantly resulted in improved nutrition and a sense of well-being. The patients gained strength, and mobility and physical activity without discomfort were possible. One patient (Case 3) had transitory relief of lumbosacral pain, but the serum acid phosphatase rose from the preoperative level of 23 to 40 Gutman units after operation; simultaneously, pain recurred and eventually there was obvious progression of the metastatic lesions. Regression of pelvic masses with improvement of micturition has resulted in 3 patients and healing of osseous lesions in the spine has been demonstrated in 1 (Case 2) five months after adrenalectomy performed four years after orchiectomy and the institution of estrogen therapy. One patient, seventeen months after adrenalectomy (Case 1), had a marked decrease in the size of the mass of neoplastic tissue palpable on rectal examination but without relief of right ureteral obstruction or of vesical obstruction, which occurred six months after operation. Removal of the right kidney for hydronephrosis and pyelonephritis was performed without incident. Subsequently, a litholapaxy and a transurethral resection of the vesical neck resulted in satisfactory emptying of the bladder. The patient has been well, without evidence of further reactivation of carcinoma, for seventeen months; the serum acid phosphatase continues to be normal (2 Gutman units per 100 cc.), and there are no demonstrable osseous metastases.

The mechanism of the sudden relief of pain after total adrenalectomy has not been explained. It has been emphasized by Huggins as the most striking result of this therapy. A profound alteration of metabolic processes that undoubtedly follows total adrenalectomy deserves further physiologic investigation. The antianabolic effect of large doses of cortisone or hydrocortisone on protein metabolism could well play a role for the short time it is in effect during the immediate postoperative period. However, the fact that the improvement is maintained when cortisone is being administered in a minimal maintenance dose suggests absence of the adrenal cortex as a factor in this improvement. Estrogens have been continued in

the management of all these patients after adrenalectomy.

A study of patients after castration and adrenalectomy has shown that on the maintenance dose of cortisone utilized, the urinary excretion of 17-ketosteroids averages 4 to 6 mg. per twenty-four hours. Biologic studies of the urine of 2 patients receiving this dose demonstrated a minimal excretion of urinary androgens.[12*] When large doses of cortisone were given there was a moderate increase of androgen excretion; however, when large doses of hydrocortisone (Compound F) were given the excretion of androgens was greatly increased. It is apparent that both urinary 17-ketosteroids and biologically active androgens may arise from the intermediary metabolism of adrenocortical 11, 17-oxygenated steroids. It is unlikely, however, that a significant quantity of androgen is derived from the small doses of cortisone ordinarily employed in substitution therapy. Furthermore, the presence of biologically active androgens in the circulation derived from administered cortisone remains to be demonstrated.

The following abstracts summarize the important details in the histories of these 7 patients with reactivated cancer of the prostate who were subjected to total adrenalectomy.

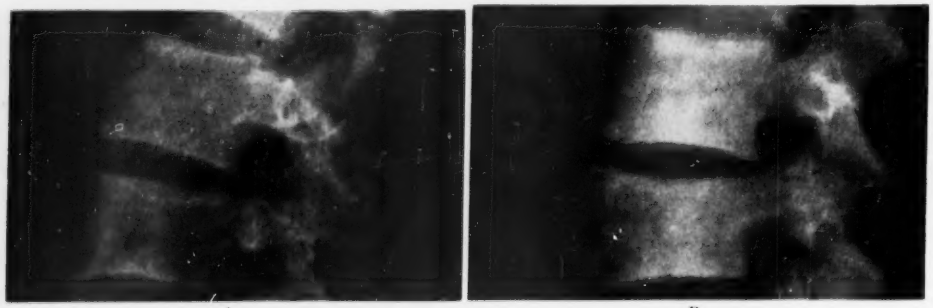
Case Reports

Case 1. N. McC. (P.B.B.H. 5B723), born on January 28, 1890, had a carcinoma of the prostate, with regional extension. Perineal prostatectomy was performed on September 24 and orchiectomy on October 1, 1949. No osseous metastases were demonstrated, and the serum acid phosphatase was 1.2 Gutman units per 100 cc. The patient was free of symptoms until January, 1951, when urinary difficulty recurred, and growth of a mass in the pelvis palpable by rectal examination indicated local reactivation of cancer of the prostate. The 17-ketosteroid excretion was found to be 10.1 mg. per 24 hours. Excretory urograms gave no evidence of function of the right kidney but demonstrated a normal renal pelvis and ureter on the left. At cystoscopic examination the right ureter was found to be obstructed 4 cm. from the bladder, and the trigone was elevated on this side by apparent recurrent prostatic neoplasm. The patient was treated with cortisone, 25 mg. daily, for 2 months without improvement but with an accompanying fall in 17-ketosteroids from 10 to 3.6 mg. per 24 hours. He was admitted to the hospital in April on account of urinary retention and obstruction of the right ureter, both caused by reactivated carcinoma with regional recurrence. Constant drainage of the bladder was necessary; no osseous metastases were demonstrated.

Bilateral total adrenalectomy and right nephrostomy were performed on May 7. At discharge the patient was receiving 25 mg. of cortisone and 4 mg. of desoxycorticosterone acetate daily and constant drainage of the urinary bladder. During the ensuing 6 months the pelvic mass diminished greatly in size according to findings by rectal palpation, but total retention of urine persisted and the right ureter remained obstructed to ureteral catheterization and excretion of Urokon and Diodrast. No osseous metastases appeared, and the serum acid phosphatase was not elevated. The patient was well and doing his chores as a farmer during this time. He was able to track a large bear in the snow for several miles, to shoot and skin it and to aid in the transportation of 300 pounds of bear meat to his home 5 miles away. (This activity occurred 6 months after total adrenalectomy.)

Because of the nonfunctioning right kidney and a draining sinus in the flank, a right nephrectomy was carried out on December 10, more than 6 months after adrenalectomy. The kidney was the site of hydronephrosis and severe pyelonephritis. One month later litholapaxy and transurethral resection were carried out. For the last 9 months the patient has continued to be completely well and actively at work as a farmer. He returns for examination every 6 weeks and receives an injection of long-acting desoxycorticosterone acetate. Cortisone has been maintained in a dosage of 25 mg. orally each day. Since adrenalectomy his weight has increased from 117 to 140 pounds, and the hematocrit from 34 to 40. He is quite well and active 17 months after adrenalectomy.

Biopsies 6 months after adrenalectomy still showed the presence of adenocarcinoma, but in some areas the histologic picture was markedly altered by both nuclear and cytoplasmic changes.



A B

Figure 1. *Roentgenograms of the Spine in Case 2.*

A = film taken in December, 1951, before total adrenalectomy, showing defects in the bodies of the third and fourth lumbar vertebras from reactivated metastatic cancer of the prostate. B = film taken in May, 1952, five months after total adrenalectomy, showing definite filling in of the defects seen in A, with calcium deposition and new bone formation that was accompanied by relief of back pain. (This change is similar to that often seen after initial orchiectomy or estrogen therapy for cancer of the prostate.)

Case 2. W. S. S. (P.B.B.H. 3A824), a 72-year-old man, had a cancer of the prostate with metastases to the spine, the diagnosis being made in December, 1947. The serum acid phosphatase measured 41.8 and 44.8 Gutman units per 100 cc. Orchiectomy was performed, and estrogens were administered, with relief of pain; the serum acid phosphatase was 4.0 Gutman units on January 8, 1948. The hematocrit rose from 38 to 40. Estrogens were continued, but back pain recurred in May, 1950. Osteoblastic metastases were demonstrated in roentgenograms of the spine and pelvis in April, 1951. The 17-ketosteroid excretion in the urine was 8.8 mg. per 24 hours.

*We are indebted to Dr. P. D. Munson, of the Department of Pharmacology, Harvard Medical School, for the measurement of urinary androgens.

Cortisone in a dosage of 37.5 mg. daily for 2 weeks and 25 mg. daily for 2 weeks afforded subjective improvement and a fall in 17-ketosteroid excretion from 8.8 to 4.9 mg. per 24 hours. Increasing pain and disability without cortisone required constant use of aspirin and codeine. Weight loss was from 182 pounds in January, 1950, to 147 pounds in December, 1951. The serum acid phosphatase rose to 11.4 Gutman units per 100 cc., and new metastases appeared in the femurs, sacrum and pelvis. The patient was confined at home by pain in December, 1951. Treatment with cortisone, again with some relief, was followed by a fall in acid phosphatase to 7.4 Gutman units and in 17-ketosteroid excretion to 3.8 mg. per 24 hours. Intravenous injection of 25 mg. of ACTH caused a rise in 17-ketosteroid excretion to 10.1 mg. per 24 hours.

Bilateral total adrenalectomy on January 3, 1952 (4 years after orchiectomy) was followed by immediate relief of pain and a fall in acid phosphatase from 7.4 to 3.2 mg. per 24 hours and of alkaline phosphatase from 8.9 to 4.2 Bodansky units. The biologically active androgen excretion before operation was about one tenth of low normal (age of 76 and 5 years postorchiectomy), and the androgen excretion was further diminished after operation. The patient was discharged from the hospital on February 16, on 25 mg. of cortisone and 0.1 mg. of estinyl daily; he had received 90 mg. of trimethyl desoxycorticosterone acetate (long acting) by intramuscular injection before discharge. He was completely symptom free for 5 months after operation. Roentgenograms of the spine and pelvis have shown striking evidence of healing by deposition of calcium in the osteoblastic metastases demonstrated 6 months earlier before adrenalectomy (Fig. 1). The hematocrit and weight, which had been 33 and 147 pounds, respectively, increased to 38 and 154 pounds in May, 1952.

Case 3. M. F. T. (P.B.B.H. 9B697), a 50-year-old man, was admitted to the hospital in November, 1950, because of carcinoma of the prostate with metastases to the pelvis and left femur. Total prostatectomy and orchiectomy were carried out in that month, and estrogens were administered. Marked improvement occurred, lasting for 3 months, but pain gradually returned in 11 months, completely disabling him in October, 1951. At that time the hematocrit was 37, the acid phosphatase 11.4 Gutman units per 100 cc., the alkaline phosphatase 4.5 Bodansky units, and the weight 87 kilograms, and diffuse osteoblastic skeletal metastases were shown in the spine, pelvis and femurs. Total bilateral adrenalectomy on November 26 was followed by relief of pain for 3 weeks; the serum acid phosphatase rose to 21.6 Gutman units at that time, to 22.4 units 1 month later and to 44.2 units 6 weeks later, with increasing pain in the back. Androgen excretion postoperatively was the same as in Case 2. Cortisone was stopped for 5 days, and minimal urinary androgens were found to persist in the 24-hour urine specimens. Cortisone dosage was increased to 100 mg. per day, giving a rise in 17-ketosteroid excretion from 2.5 mg. to 6.8 mg. per 24 hours and a moderate rise in androgen excretion. The serum acid phosphatase decreased from 44.2 to 29.8 Gutman units during this period of large dosage, rising to 40 units when the cortisone dosage was reduced to 25 mg. Compound F, 300 mg. a day, caused a rise in 17-ketosteroid excretion from 6 to 47 mg. per 24 hours in 5 days and a striking rise in androgen excretion, which returned to a minimal level with a return to cortisone dosage of 50 mg. a day. The serum acid phosphatase decreased from 40 to 22.8 Gutman units during administration of Compound F, and there was simultaneous symptomatic relief.

This patient did not show any substantial improvement after adrenalectomy and actually was better subjectively and objectively only temporarily while receiving massive cortisone substitution therapy. A second course of 300 mg. of cortisone a day for 5 days resulted in a fall of serum acid phosphatase from 35 to 23 Gutman units per 100 cc., with accompanying subjective improvement. However, after 6 weeks of 100 mg. of cortisone a day, pain had recurred, and the acid phosphatase had risen to 73.2 Gutman units and the alkaline phosphatase to 9.1 Bodansky units. His condition subsequently deteriorated steadily, accompanied by a rise in acid phosphatase to 154 Gutman units. X-ray therapy locally gave some relief of pain. He died of disseminated cancer 7 months after total adrenalectomy and 19 months after prostatectomy and orchiectomy. Post-mortem examination showed diffuse carcinomatosis involving retroperitoneal nodes in the pelvis and around the aorta and vena cava, and multiple hepatic and osseous metastases.

This case illustrates the biologic variables to be expected in the course of profound alterations of protein, carbohydrate and electrolyte metabolism in the treatment of cancer. Although 6 patients with reactivated cancer of the prostate have been definitely improved after total adrenalectomy, this patient showed no sustained benefit and was ultimately worse, though his condition was undoubtedly out of control prior to adrenalectomy. It is noteworthy that he was the youngest patient in the series and had the poorest response to orchiectomy and estrogens, and little response to adrenalectomy.

Case 4. E. B. (P.B.B.H. 6E313), a 60-year-old man, was first seen in September, 1951, because of carcinoma of the prostate obstructing the rectum and bladder, with regional extension and osseous metastases. Orchiectomy* was performed in that month, and stilbestrol was given, the dosage of 12.5 mg. a day being increased to 25 mg. in January, 1952. Congestive heart failure and hypertension complicated the picture. The patient was referred to the Peter Bent Brigham Hospital in March, when the acid phosphatase was 2.4 Gutman units per 100 cc., the alkaline phosphatase 3.3 Bodansky units, and 17-ketosteroid excretion 6.3 to 9.1 mg. per 24 hours, rising to 15.3 mg. after intravenous injection of 25 mg. of ACTH. Constant drainage of the bladder was necessary. Osteoplastic metastases in the pelvis were demonstrated. Left adrenalectomy was performed on March 17, and colostomy on April 4 because of partial obstruction of the bowel. The patient's condition slowly improved after colostomy, but considerable trouble with diarrhea was encountered. Right adrenalectomy on May 14 was uneventful. After 2 weeks the patient was able to urinate with ease, and constant drainage of the bladder was stopped. He was discharged 16 days after the second adrenal operation, when he was receiving 37.5 mg. of cortisone and 0.1 mg. of estinyl a day. Perineal pain was relieved, and on rectal examination the mass in the pelvis showed diminished encroachment on the rectum by the encircling prostatic neoplasm 4 months after operation. The patient is definitely improved in every respect, but a longer period of observation is necessary for ultimate assessment of the result. Thus far, there has been no evidence of progression of the neoplastic process.

Case 5. R. T. (P.B.B.H. 6A38), a 62-year-old man, was seen in February, 1947, because of carcinoma of the prostate with regional extension, being treated with estrogens elsewhere. He was admitted to the Peter Bent Brigham Hospital in May, and total perineal prostatectomy and bilateral orchiectomy were performed. Regional but not distant metastases were found, and the serum acid phosphatase was 4.2 Gutman units per 100 cc. Estinyl, 0.1 mg. daily, was prescribed, and the patient was well for more than 3 years. The serum acid phosphatase was 0.6 Gutman units per 100 cc. in October, 1950, but regional recurrence and osseous metastases were demonstrable. He also had congenital polycystic disease of the kidneys and hypertensive vascular disease. With spreading metastases in the ilia, spine and femurs increased doses of Dilaudid were necessary for control of pain in 1951–52. In April, 1952, the serum acid phosphatase was 7.8 Gutman units per 100 cc., and the patient was unable to carry on his work as an ophthalmologist. There was extensive involvement of the right acetabulum. The 17-ketosteroid excretion had risen from 8 to 14.5 to 17.4 mg. per 24 hours.

Bilateral total adrenalectomy was done on April 15. The patient was ambulatory within 1 week and without pain or necessity for narcotics. At discharge from the hospital on May 15, he was greatly improved both subjectively and objectively. Improved mobility of the spine and hips was impressive. Adduction of the femurs could be done without pain, and he walked without his former limp. The blood pressure, previously 220/120, was stable at 160/90. Maintenance substitution therapy consisted of 37.5 mg. of corti-

*Performed by Dr. Donald Marshall, of Portland, Maine.

sone a day and trimethyl desoxycorticosterone acetate, 75 mg. intramuscularly, to last 1 month. Estrogens in the form of TACE (tri-p-anisylchloroethylene), 24 mg. a day, are being administered. Complete relief of pain in the spine and hips has lasted for 5 months and regression of the pelvic mass is apparent on rectal examination. The patient reported that he was well and at work in September, 1952.

CASE 6. J. H. T. (P.B.B.H. OD306), a 59-year-old man, was seen on July 6, 1949, because of carcinoma of the prostate with regional extension. Perineal subtotal prostatectomy was performed on July 11, and bilateral orchiectomy in October. The serum acid phosphatase was 1 Gutman unit per 100 cc. at this time, and the lumbar spine and pelvis showed no evidence of metastases. He was treated with estinyl, 0.1 mg. daily. Persistent pain in the lower back began in June, 1951, and x-ray examination showed osteoblastic metastasis involving the entire body of the 4th lumbar vertebra. Treatment with cortisone, 25 mg. daily for 1 month, gave some relief of pain temporarily, but subsequently large doses of aspirin and codeine were frequently necessary. X-ray therapy locally gave transitory relief of back pain in August. Continued use of sedatives and increased pain necessitated admission to the hospital in March, 1952. The serum acid phosphatase was 3 Gutman units per 100 cc., and the alkaline phosphatase was 5.0 Bodansky units. X-ray examination again showed osteoblastic metastases in the lumbar spine. A two-stage bilateral total adrenalectomy was completed on April 22. Complete relief of pain has been achieved, and no sedation has been necessary since operation. The patient feels greatly improved and has been at home for 5 months on cortisone, 37.5 mg. per day. He receives 30 mg. of trimethyl desoxycorticosterone acetate intramuscularly (long acting) once a month, and TACE, 12 mg. daily. He has been seen twice a month in follow-up study and continues to show definite improvement, with apparent control of cancer. The serum acid phosphatase was 4.6 Gutman units per 100 cc. in September, 1952.

A B

FIGURE 2. *Roentgenograms of the Left Femur in Case 7, Showing the Pathologic Fracture of the Upper Shaft Four Weeks after Intramedullary Fixation* (A) *and Eight Weeks after the Fracture and Four Weeks after Total Adrenalectomy* (B). *Definite evidence of healing of the fracture is apparent. Clinical correlation was subsequently manifest by active mobility of the limb and beginning of weight bearing.*

CASE 7. J. S. C. (P.B.B.H. 8B199), a 61-year-old man, was seen on February 1, 1951, because of carcinoma of the prostate obstructing the urethra and rectum, with regional and inguinal metastases. An abdominoperineal resection of the rectum, with total prostatectomy and seminal vesiculectomy, was carried out on February 6.* Estrogen therapy was followed by a decrease of acid phosphatase from 13.4 to 6.2 to 1.2 Gutman units per 100 cc. in 1 month. Osteoblastic metastases were visible in both innominate bones on March 20. Bilateral orchiectomy was performed on June 14, when the serum acid phosphatase was 3.8 Gutman units per 100 cc.

The patient did well in spite of spreading osseous metastases until June 2, 1952, when investigation of pyuria led to cystoscopic discovery of vesical calculi. Litholapaxy was performed 4 days later. The serum acid phosphatase was 102 Gutman units per 100 cc., and the alkaline phosphatase 18.1 Bodansky units at this time. Films of the spine, pelvis and femurs showed widespread osseous metastases.

Owing to increasing pain and rising serum acid phosphatase the patient was recalled for cortisone therapy and possible adrenalectomy. He returned on July 1, and cortisone in a dosage of 100 mg. daily, was started. On July 5 he sustained a pathologic fracture of the left femur and underwent open reduction and intramedullary fixation.† Metastatic cancer was found in the fracture site. The serum acid phosphatase on July 1 was 330 Gutman units per 100 cc. After 100 mg. of cortisone daily for 2 weeks the serum acid phosphatase was 5.8 Gutman units, and the alkaline phosphatase 14.5 Bodansky units. Pain had been relieved after a few days of cortisone therapy. The blood sugar rose to 153 mg. and later to 177 mg. per 100 cc. Seventeen days after the fracture and fixation of the femur, a bilateral total adrenalectomy was performed. The postoperative course was uneventful. Roentgenograms 3 weeks after fracture showed evidence of healing of the fracture site (Fig. 2). The patient became ambulatory on crutches 2 weeks after operation and was discharged 2 weeks later on a maintenance daily dose of 37.5 mg. of cortisone orally and on long-acting trimethyl desoxycorticosterone acetate to be given intramuscularly 45 mg. each month. The serum acid phosphatase was 6.1 Gutman units per 100 cc. at the time of discharge from the hospital (Fig. 3). Progress and relief of symptoms have been impressive during the last month at home. Full range of motion of the left leg has been accomplished along with ambulation on crutches and beginning of weight bearing. The hyperglycemia noted during the period of excessive cortisone therapy was at first attributed to the gluconeogenesis caused by the steroid. It is now evident, however, that a previously unsuspected diabetes mellitus was brought to light.

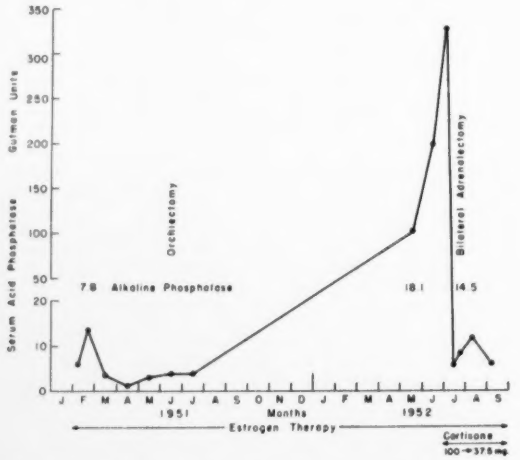


FIGURE 3. *Changes in Serum Acid Phosphatase in Case 7 over a Period of Twenty Months in Advanced Cancer of the Prostate from the Beginning of Estrogen Therapy to Orchiectomy Followed by Reactivation and Subsequent Regression with Cortisone Therapy and Adrenalectomy.*

*Operation performed by Drs. Francis D. Moore and J. Hartwell Harrison.

†Performed by Dr. T. B. Quigley.

Hormonal Therapy before, during and after Total Adrenalectomy

The night before operation the patient is given 100 mg. of cortisone acetate by intramuscular injection, and this is repeated at 7 o'clock the next morning. The use of adrenocortical extract during operation is no longer employed, but either cortisone or hydrocortisone (Compound F) is given intravenously at an infusion rate of approximately 10 mg. per hour during the operative procedure and for a period of six to eight hours immediately thereafter. This assures a peak level of circulating adrenocortical hormone during the time of maximal hormone requirement.

If necessary, as indicated by a significant and persistent fall in blood pressure, Neo-Synephrine is added to the intravenous infusion, the dosage being adjusted to maintain the blood pressure above 140 systolic, 100 diastolic, in hypertensive and above 100 systolic, 70 diastolic, in normotensive patients. It appears that the continuous intravenous infusion of pure adrenocortical steroids may well decrease the need for vasopressor agents. After operation, cortisone acetate, 50 mg. every six hours, is given intramuscularly for the first forty-eight hours; thereafter, the dose is gradually diminished over a period of six to ten days to the maintenance level of 25 to 37 mg. a day by mouth.

Postoperatively, all urine is collected, and studies are made each day of sodium chloride excretion. Desoxycorticosterone acetate 1 to 3 mg. a day is given when necessary to avoid sodium chloride depletion, and 3 to 8 gm. of salt is added to the diet to meet the individual demands. There has been little actual change in the management of these patients from the regimen described one year ago.

The patients being treated for cancer have presented much less of a problem from the standpoint of substitution therapy than the hypertensive patients or those with Cushing's syndrome (the majority of whom have elevated blood-pressure levels). Unlimited salt and a generous allowance of desoxycorticosterone acetate are possible in cases of cancer, giving greater security without contributing any undesirable metabolic factor. On the other hand, larger doses of cortisone are permissible in hypertensive patients but undesirable in those with cancer or hyperadrenalism. In each case it is necessary to establish the demands for substitution therapy.

Summary and Conclusions

Further efforts at control of cancer of the prostate by means of adrenal inhibition with cortisone, hydrocortisone and total adrenalectomy are described. Relief of pain has been accomplished in more than half the patients so treated for periods of four to nine months and control of reactivated cancer, with sustained regression for seventeen months in 1 case.

Objective signs of improvement were better nutrition, increased strength and activity, diminished serum acid phosphatase, decrease in the size of soft-tissue masses, relief of urinary obstruction and roentgenographic evidence of healing of osseous metastases even after pathologic fracture. The changes in urinary 17-ketosteroid and androgen excretion after cortisone therapy and after adrenalectomy in castrated males are enumerated.

The apparent subjective and objective improvement of patients after total adrenalectomy has indicated at least a temporary biologic arrest of the progress of cancer of the prostate. The evidence available today seems to signify that this arrest is accomplished by means of altered metabolic processes pursuant to changing of the hormonal environment of the neoplastic cell.

Similar, though less striking, improvement has been observed after adrenalectomy for reactivated cancer in comparison to the initial orchiectomy and estrogen therapy. It is significant that an effect on the biologic behavior of certain cancers by the action of the adrenocorticosteroids has been demonstrated.

The complete elimination of biologic androgens in the urine was not accomplished by orchiectomy and total adrenalectomy, though significant reductions were observed. Androgens were still demonstrable in the urine when cortisone had been stopped for five days. Androgen and 17-ketosteroid excretion were both increased when doses of 100 to 300 mg. of cortisone acetate or hydrocortisone were administered to the orchiectomized and adrenalectomized patient.

The role of the adrenal cortex and the corticosteroids in the growth of prostatic and other forms of cancer, especially those of endocrine and endocrine-controlled organs, demands further investigation.

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ACUTE INFECTIOUS LYMPHOCYTOSIS*

Report of Two Cases in the Same Family

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INFECTIOUS lymphocytosis, originally thought to be a variant of infectious mononucleosis, was first described and named by Smith[1] in 1941. Its chief characteristic is a benign, relative increase in the number of the small mature lymphocytes in the peripheral blood and in the bone marrow. Original reports listed few or no clinical manifestations, these observations being based on cases from institutions where marked lymphocytosis was considered to be the only unusual characteristic. More recently, however, a wide variety of clinical patterns have been reported in this disease. Smith believes that the disease has a specific infectious basis; he has reported 3 cases occurring in one family.[2] Lorenz and Hardy[3] described cases occurring almost simultaneously in 2 brothers. The following case report concerns the occurrence of this condition in 2 children in the same family.

CASE REPORTS

CASE 1. R. E. F., a 4-year-old boy, had been followed since August, 1951, chiefly for recurrent bouts of bronchial asthma. The white-cell count on August 10, 1951, was 8300, with a normal differential. On October 28 he was seen because of an acute exacerbation of bronchial asthma. At this time the white-cell count was 11,300. The histoplasmin and tuberculin tests were both negative. On February 7, 1952, he was seen because of a right inguinal hernia. The white-cell count at another hospital before herniorrhaphy was reported as 9000. On February 13 the histoplasmin and tuberculin tests were again negative. He was brought to the clinic with typical measles on March 10, when the white-cell count was 4100. On June 13 he was seen because of a typical asthmatic attack, which had begun with symptoms of rhinorrhea and wheezing 3 days previously. There had been no other symptoms, but the mother believed that the wheezing had been more severe than usual.

TABLE 1. *Peripheral-Blood Studies in Case 1.*

DATE	WHITE-CELL COUNT	LYMPHOCYTES	HEMOGLOBIN
		%	*gm./100 cc.*
Aug. 17, 1951	8,300	58	12.5
Oct. 28, 1951	11,300		
Feb. 7, 1952	9,000	61	
Mar. 10, 1952	4,100		12.0
Jun. 13, 1952	32,800	88	12.8
Jun. 15, 1952	29,500	84	12.8
Jun. 18, 1952	28,000	85	12.5
Jun. 22, 1952	25,750	76	12.8
Jun. 27, 1952	21,000	74	12.0
Jul. 2, 1952	17,000	76	—
Jul. 9, 1952	9,000	64	—
Jul. 31, 1952	8,100	60	12.8
Aug. 13, 1952	7,800	59	12.0

Physical examination revealed a well developed and well nourished boy who appeared acutely ill, with a temperature of 101°F., and in moderate respiratory distress. The skin was clear; there were shotty cervical lymph nodes that had not increased appreciably in size over previous examinations, but there was no generalized lymphadenopathy. The nasal mucosa and pharynx were slightly injected. The neck was supple. Expirations were prolonged, and both lung fields were filled with sonorous and musical rales and wheezes. The heart was normal. The liver edge was just palpable, and the tip of the spleen was barely palpable below the left costal margin. A throat culture taken at this time was subsequently reported as showing nonhemolytic streptococci and *Staphylococcus aureus*. A nasopharyngeal culture taken 18 hours later on Bordet–Gengou medium failed to grow out *Haemophilus pertussis*.

Examination of the blood showed a white-cell count of 32,800, with 88 per cent lymphocytes, 6 per cent neutrophils and 6 per cent eosinophils. The lymphocytes were all small or intermediate in type and appeared normal.

The patient had never had pertussis, but there had been no known recent exposure to the disease. He had been immunized against pertussis and had received a recall immunization 9 months previously. A heterophil-antibody agglutination taken at this time was subsequently reported as negative. Histoplasmin and tuberculin skin tests were also negative, and x-ray films of the long bones were interpreted as normal.

On epinephrine, aminophylline, expectorants and oral administration of penicillin there was a gradual improvement in the asthma but no significant change in the appearance of the pharynx. Two days later the white-cell count was 29,500, with 84 per cent lymphocytes. Urinalysis was normal. A tibial-bone-marrow aspiration revealed a total count of 154,000 nucleated cells per cubic millimeter; the neutrophils consisted of 14 per cent band forms, 9 per cent segmented forms and 16 per cent myelocytes, and the lymphocytes of 32 per cent small, 9 per cent intermediate, 4 per cent eosinophilic and 16 per cent erythrocytic series. The bone marrow appeared somewhat hyperplastic, with a lymphocyte count of 43 per cent. The lymphocytes were small and mature and did not appear abnormal. The differential counts are presented in Table 1.

On the basis of the leukocytosis with lymphocytosis and no evidence of other diseases producing a similar hematologic picture it was decided that the patient had infectious lymphocytosis. The mother was requested to bring the remaining members of the family for hematologic studies; one of these was the patient in Case 2.

In the ensuing 5 days there was a gradual clearing of the asthmatic picture, as well as of the nasopharyngitis. Five days after the initial blood studies, the white-cell count had dropped to 25,750, with 76 per cent lymphocytes. The count did not return to normal until July 9, however (Table 1) — 26 days after the leukocytosis was initially noted. Since the patient was followed as an outpatient, it was not practical to obtain a daily hemogram, and it is therefore possible that the blood picture returned to normal at some time between July 2 and July 9. A repeat heterophil-antibody agglutination on June 27 was reported as negative. The pharyngeal inflammation was not noticeably influenced by oral administration of penicillin for 4 days, and the tip of the spleen was still barely palpable after 26 days.

*From the Pediatric Clinic, Base Hospital, Stewart Air Force Base, Tennessee.

CASE 2. P. F. F., the 3-year-old brother of the patient in Case 1, had been followed at irregular intervals since October, 1951, for various minor complaints. The only previous blood examination, which had been performed on October 24, was reported as showing a white-cell count of 9150, with 60 per cent lymphocytes, and a hemoglobin of 12.8 gm. per 100 cc. The patient was seen on June 14, having been brought to the clinic for examination as requested because of the lymphocytosis discovered in his brother. The mother had noted no subjective symptoms except mild anorexia and rhinorrhea for the past few days.

Physical examination demonstrated a well developed and well nourished boy, who did not appear ill despite a temperature of 102°F. by rectum. The examination was entirely normal except for a diffuse infection of the posterior pharynx, without exudate. The spleen was not palpable.

Examination of the blood revealed a white-cell count of 29,750, with 83 per cent lymphocytes, which were small and appeared mature. Histoplasmin and tuberculin skin tests were negative. Throat culture was subsequently reported as showing *Neisseria catarrhalis* and *Staph. aureus* and no growth on Bordet-Gengou medium. Heterophil-antibody agglutination was subsequently reported as negative. The patient had never had pertussis; there had been no recent exposure, and he had received complete immunizations against pertussis, the last recall immunization having been given 9 months previously. No bone-marrow aspiration was done.

On the basis of the hematologic findings, it was believed that this patient also had infectious lymphocytosis, and it was decided to treat him supportively with aspirin and bed rest. Two days later the temperature was 101°F. by rectum, and there was no decrease in the signs of pharyngeal infection. The tip of the spleen was questionably palpable. The white-cell count was 27,500, with 81 per cent lymphocytes. Since there had been little change in the clinical and hematologic picture over a 2-day period without specific therapy, it was decided to try a broad-spectrum antibiotic in an effort to obtain a change in the leukocytosis. Aureomycin therapy, 125 mg. every 4 hours for 6 doses and 125 mg. every 6 hours for 3 days, was begun on June 16. Two days later the temperature was 100.8°F. by rectum. The mother noted no subjective improvement, and the appearance of the pharynx was unchanged. The white-cell count at this time was 27,000, with 80 per cent lymphocytes. On June 22 the temperature was normal; anorexia had persisted, but there was some diminution in the pharyngeal inflammation. However, the white-cell count remained elevated at 26,650, with 79 per cent lymphocytes. In the following 5 days there was a complete clearing of the pharyngeal inflammation, and the patient remained afebrile and asymptomatic. The white-cell count did not return to normal until July 9 (Table 2).

TABLE 2. *Peripheral-Blood Studies in Case 2.*

DATE	WHITE-CELL COUNT	LYMPHOCYTES	HEMOGLOBIN
		%	*gm./100 cc.*
Oct. 24, 1951	9,150	60	12.8
Jun. 14, 1952	29,750	83	12.2
Jun. 18, 1952	27,000	80	12.5
Jun. 22, 1952	26,650	79	12.0
Jun. 27, 1952	25,000	76	13.0
Jul. 2, 1952	19,150	71	
Jul. 9, 1952	9,950	63	13.0
Jul. 31, 1952	7,850	55	12.6

Again, because this was an outpatient, no blood studies were done between July 2 and July 9. A repeat heterophil antibody agglutination on June 27 was negative.

Findings in Other Members of the Family

R. H. F., a 16-month-old sibling, had been followed since August, 1951. On August 17 examination of the blood, performed because the patient had acute otitis media and gastroenteritis, showed a white-cell count of 15,800, with 56 per cent lymphocytes, and a hemoglobin of 9 gm. per 100 cc. On November 19 the white-cell count was 8650, and the hemoglobin was 10.2 gm. On May 16, 1952, the hemoglobin was 11.3 gm., and the white-cell count 10,000. On June 14, when the patient was brought in for examination, the white-cell count was 6000, with 56 per cent lymphocytes. On June 18 the white-cell count was 9000.

Mrs. A. F., the 23-year-old mother of these children, was found to have no pharyngitis or other abnormalities on June 14, 1952. The white-cell count was 6300, with 42 per cent lymphocytes at this time, and on June 22 the white-cell count was 7000, with 40 per cent lymphocytes.

Sgt. P. E. F., the 26-year-old father of the children, was found to be entirely normal upon examination on June 15, 1952. The white-cell count was 10,000, with 31 per cent lymphocytes. Repeat counts were 9150, with 30 per cent lymphocytes, on June 22 and 8650, with 35 per cent lymphocytes, on July 9.

DISCUSSION

Smith[1] believes that there is both an acute and a chronic type of infectious lymphocytosis. He has summarized the evidence for the establishment of infectious lymphocytosis as a specific entity.[2]

Etiology and Epidemiology

Repeated bacterial and viral studies have revealed no causative agent. Smith[2] reported 4 cases in 1944, 3 cases in members of the same family and the fourth case a hospital contact. His data suggest an infectious etiology, with an incubation period of twelve to twenty-one days. In addition to Smith's report, Lorenz et al.[3] described cases occurring almost simultaneously in brothers; in this report the disease developed in 2 brothers in a family of 5. Epidemics have been observed in children's institutions.[4, 5] Most of the cases have been in children, but Duncan[6] reported 2 cases in young adults. The degree of communicability and immunity has not been determined. The disease was originally reported only from the United States and England, but subsequent cases have been reported from Uruguay, Finland and Switzerland.[4] Apparently, there is no racial predilection or seasonal incidence.[7]

Pathology

Smith described lymph-node biopsies in 2 cases. There was analogous follicle degeneration and reticuloendothelial proliferation in the sinuses of the lymph nodes. In another report the follicles were described as usually small and occasionally showed hyalinization.[7]

Clinical Manifestation

The earlier reports attributed few or no symptoms to the disease. More recently, however, various complaints have been noted, along with diverse physical findings. The majority of patients have exhibited manifestations of infections of the upper respiratory tract, but no specific or similar pathogenic organisms have been cultured. The clinical course may range from mild or no symptoms through moderate to a severe course. Case 1, reported above, showed typical signs of bronchial asthma and nasopharyngitis, but, although the mother believed that the asthmatic symptoms were more exaggerated during this episode, there was no objective evidence of any significant difference

from previous bouts of asthma. Case 2 showed severe inflammation of the pharynx that was apparently not affected by aureomycin. In most cases the lymph nodes and spleen are not significantly enlarged. In Case 1 the tip of the spleen was palpable, but this was not considered to be a significant enlargement.

Abdominal pain has been frequently reported as a symptom of this disease, the character varying from mild and transient to severe enough to simulate a surgical emergency, although the latter cases are rare.[8] The pain is usually colicky and periumbilical, and the abdomen remains soft. The incidence of abdominal pain in association with throat infections in children is well known.[9] However, this mesenteric or retroperitoneal lymphadenitis is usually associated with less rise in the total white-cell count and more neutrophilic response than that seen in infectious lymphocytosis. Vomiting is not uncommon, and associated diarrhea has been reported.[4]

In recent years several cases with symptoms and signs referable to the central nervous system have been noted. Thelander and Shaw[10] described encephalitic manifestation in 2 cases of what they believed was infectious mononucleosis but would more probably at this time be diagnosed as infectious lymphocytosis. The resemblance to poliomyelitis has also been observed.[11] A slight spinal-fluid pleocytosis has been noted.[6, 10] There were no meningeal symptoms or signs in the cases reported above, and no lumbar puncture was performed.

An extensive morbilliform rash was observed in 1 adult patient.[6]

In some of the cases reported as epidemics of the disease from children's institutions, the patients have been completely asymptomatic.[12] In most cases it has been diagnosed on routine hematologic studies. Thus, any clinical manifestations present are usually those frequently observed in many other diseases of childhood-fever, signs of upper-respiratory-tract infection, abdominal signs and occasionally neurologic manifestations. A comprehensive review of the clinical picture of this condition is presented by Meyer.[7]

Laboratory Data

The sole characteristic is the hyperleukocytosis, the increase being practically confined to the lymphocytic series. Meyer[7] reports the range of the white-cell count to be from 22,500 to 120,000. Most authors have recorded a count of about 40,000. The maximum count was 32,800 in Case 1 and 29,750 in Case 2. In the Milwaukee epidemic the range of the count was 18,900 to 147,000.[4] The lymphocytic elements range from 62 to 97 per cent.[4, 7] Lymphocytes made up 88 per cent of the differential white-cell count in Case 1 and 83 per cent in Case 2 at the height of the disease. The lymphocytes are small and mature appearing, with a thin rim of cytoplasm. The leukocytosis usually lasts from two to five weeks in children, but persistence for seven months has been reported.[7] The erythrocytes, hemoglobin and platelets are not disturbed.

The bone marrow is hyperplastic, with an increase of mature lymphocytes but with no abnormality of the granulocytic or erythrocytic series. The total count of nucleated cells in the tibial bone marrow in Case 1 was 154,000, with 41 per cent lymphocytes. The bone-marrow changes gradually disappear as the patient improves, but apparently persist longer than the abnormalities in the peripheral blood.

The heterophil-antibody agglutination (Paul–Bunnel test) is negative in true cases of infectious lymphocytosis and is the main point in distinguishing it from a closely similar disease, infectious mononucleosis. The agglutination was negative on two occasions in each of the cases reported above.

The Wassermann reaction is negative in this condition, and much fewer false-positive reactions occur, in contrast to infectious mononucleosis.

No significant bacteriologic findings were noted in either case, as in those described by others.

Virologic studies in Smith's[2] cases were not revealing.

Differential Diagnosis

Several conditions occurring in childhood, and producing a leukocytosis, chiefly of the lymphocytic elements, must be differentiated.

Infectious mononucleosis is common in children and may be confusing. In fact, some of the earlier cases of infectious lymphocytosis were reported as atypical examples of infectious mononucleosis.[10, 12] The clinical picture may be similar although the patient with infectious mononucleosis generally shows severe throat involvement, fever, marked malaise, generalized lymphadenopathy, splenomegaly and occasionally rash and jaundice. The main distinguishing features are the presence of large, abnormal lymphocytes or mononuclear cells and a positive heterophil-antibody agglutination in infectious mononucleosis; in infectious lymphocytosis, the lymphocytes are usually small and mature appearing in contrast. The comprehensive reports of Smith[1] and Bernstein[13] describe the histologic features of the lymphocytes in infectious mononucleosis. In the cases presented above, no abnormal cells were observed, and the heterophil-antibody reaction was negative on two occasions in each patient.

Pertussis may produce a marked lymphocytosis.[14] Leukocytosis of the degree caused by infectious lymphocytosis is usually seen only in the severe case of pertussis, in which the clinical symptoms are characteristic. Patients with clinically mild and atypical pertussis rarely have an extreme leukocytosis. Cultural confirmation affords a conclusive diagnosis. In Case 1, although the maximum

white-cell count was 32,800, pertussis was ruled out by failure of *H. pertussis* to grow on Bordet–Gengou medium and absence of any suggestive clinical picture. Pertussis was eliminated by the same means in Case 2. Lymphocytosis is apparently not caused by administration of pertussis vaccine.[14]

In the early stages lymphatic leukemia, especially the acute type, may be suggested. The clinical picture of fever, lymphadenopathy, splenomegaly, hemorrhagic tendencies and progressive downhill course are usually sufficient to indicate the diagnosis. The presence of lymphoblasts in the peripheral blood and bone marrow, the diminution in erythrocytes, hemoglobin and platelets in leukemia are the most reliable distinguishing laboratory aids. In addition, roentgenograms of patients with leukemia frequently show osseous changes,[15] which were absent in Case 1. It should be remembered that in the occasional case of leukemia, the patient may be followed for a relatively long period without bleeding tendencies, lymphadenopathy, splenomegaly and anemia. The long-standing case of chronic infectious lymphocytosis may cause a mild anemia, or anemia may be due to iron deficiency or some other condition. Careful clinical evaluation and study of the bone marrow usually serve to differentiate the two conditions.

An acute surgical condition of the abdomen may be simulated by the clinical pattern.[8] Duncan[6] has observed a relative and absolute lymphocytosis during treatment of a child with purulent otitis media with sulfadiazine. The lymphocytosis cleared promptly when the drug was discontinued. I have also noted such a response after treatment of otitis media with a triple sulfonamide mixture. Occasionally, a viral encephalitis or poliomyelitis simulates infectious lymphocytosis.[11] Typhoid fever, tuberculosis and brucellosis can be ruled out by appropriate tests. A lymphocytosis occasionally occurs in infections ordinarily accompanied by neutrophilic increase. Postinfectious lymphocytosis after influenza and other infections in children has been encountered.[1] With the recent interest in virology it is anticipated that further light will be thrown on certain viral diseases, including the leukocytic response in such infections.

Course and Prognosis

Smith[1, 2] describes both acute and chronic types of the disease. The symptoms, if present, are usually of much shorter duration than the hematologic abnormalities. Most of the cases show an abnormal leukocyte elevation for two to five weeks, but lymphocytosis as long as seven months has been noted. In both the cases reported above, the white-cell count remained elevated for nineteen to twenty-six days. The prognosis is excellent, and although the patient is extremely ill in isolated cases, complete recovery without residua is the rule.

Treatment

In the patient with clinical symptoms, symptomatic treatment is indicated. Control of fever and management of respiratory or any other symptoms present should be carried out. Chemotherapy or antibiotics apparently do not alter the course of the disease, as demonstrated by the lack of effect of penicillin in Case 1 and of aureomycin in Case 2.

Summary

Two cases of acute infectious lymphocytosis occurring almost simultaneously in brothers are described. Both patients showed signs of upper respiratory infections, and the course was not affected by penicillin in 1 case or by aureomycin in the other. The maximum white-cell counts were 32,800 and 29,750. The leukocytosis persisted between nineteen and twenty-six days in both cases. Bone-marrow studies in 1 case revealed only hyperplasia of the lymphoid elements.

Other diseases frequently confused with infectious lymphocytosis were eliminated by appropriate means.

The syndrome of infectious lymphocytosis is reviewed.

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DRUG FEVER DUE TO QUINIDINE*

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HYPERSENSITIVITY to quinidine is not rare, the symptoms usually taking the form of gastrointestinal disturbances or other reactions similar to those produced by its levo-isomer, quinine. Rarer manifestations include thrombocytopenia, skin rashes and fever.

Although all drugs probably can act as allergens, some appear to induce hypersensitivity more readily than others, and only a few oral medications are known to produce drug fever. These include the antipyretics, sulfonamides, the thiouracil derivatives and quinine. Fever as a reaction to quinidine is rare. Since Frey[1] introduced quinidine for the treatment of auricular fibrillation more than thirty years ago few cases have been reported in the literature. Levy,[2] in 1922, reported fever in 2 patients who received quinidine. In 1942 Sturnick[3] first drew specific attention to a predominantly febrile reaction to the drug. Siegal and Horn,[4] in 1950, reported a case of quinidine allergy in which there was a generalized pruritic maculopapular rash accompanied by a mild elevation in temperature. In 1951, 2 cases of fever followed the use of quinidine, as noted by Stimson and McKusick.[5] Two cases were recently reported by Berley and Saland.[6]

Of these patients only 5 had elevations of temperature in the range of 103 to 104°F. It is therefore interesting that, in one year, we observed 3 patients with marked hyperpyrexia in whom a diagnosis of quinidine drug fever could be established.

Case Reports

Case 1. K. M., a 40-year-old woman, was admitted to the hospital on April 24, 1950, because of malaise and generalized vague aches and pains. A low-grade fever had been noted. For 2 weeks she had been taking 0.2 gm. of quinidine sulfate once daily on the advice of her physician for annoying "skipped beats" but had discontinued dosage 2 days previously. Earlier in life she had suffered from hay fever.

On the 2d day the temperature was normal, but because of recurrence of disturbing ventricular premature contractions, quinidine was again ordered in a dosage of 0.2 gm. 3 times a day. Four hours after the initial dose the temperature began to rise rapidly, accompanied by a chill, reaching 104.4°F. 3 hours later. Fever persisted, and there was a secondary rise to 104.2°F. 24 hours thereafter. The patient complained of chills, headache, tinnitus and back pain, and reported a transient, pruritic, macular rash shortly after quinidine had been readministered. She recalled a similar episode 3 days before admission.

This suggested an allergic reaction to quinidine, and the drug was stopped after 3 doses (a total of 0.6 gm.), pyribenzamine being substituted. The temperature began to fall immediately and reached normal 48 hours after the last dose of quinidine.

During the febrile episode, the white-cell count was elevated, the sedimentation rate was 40 mm. in 1 hour (Westergren method), and urine and blood cultures were sterile. Tests for febrile and cold agglutinins were negative.

On the 8th hospital day a test dose of 0.1 gm. of quinidine sulfate was administered. The temperature rose promptly, reached a peak of 103.4°F. 6 hours after the test dose, and fell to normal in 24 hours. The rise in temperature was accompanied by vomiting and tinnitus. The effect of quinidine on the temperature is shown in Figure 1.

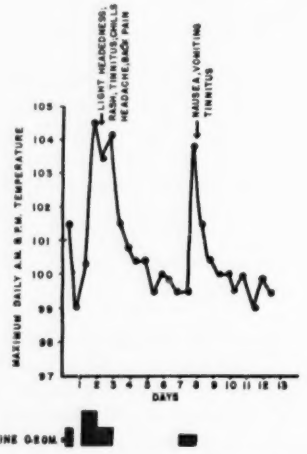

Figure 1. *Effect of Quinidine on the Temperature in Case 1. Fever was subsiding on admission, two days after quinidine was stopped. The temperature rose rapidly after readministration of the drug for two days and fell promptly after it had been discontinued. The same reaction occurred, after a four-day interval, when a single dose of 0.1 gm. of quinidine was given.*

An intradermal skin test with 0.1 gm. of quinidine hydrochloride produced an erythematous area with pseudopodia of 1.25 by 2.45 cm. 15 minutes later. After 1 hour a pale, raised area, with pseudopodia of approximately 2.0 by 1.25 cm., was present. No similar reaction appeared in a normal test subject. A skin patch test produced no skin reaction.

Case 2. T. G., a 60-year-old man, was admitted to the hospital because of arteriosclerotic and hypertensive heart disease, and mild congestive heart failure of 2 weeks' duration. An electrocardiogram revealed auricular flutter with a 2:1 auriculoventricular block. He had been digitalized, and on the 2nd hospital day, because of persistent premature contractions, was given quinidine sulfate, 0.2 gm. every 3 hours, in addition to maintenance doses of Digoxin. After 9 doses of quinidine (a total of 1.8 gm.), a nonpruritic, maculopapular rash appeared on the abdomen and thighs; quinidine was discontinued.

On the 7th hospital day auricular fibrillation was noted. In an effort to convert the auricular fibrillation, Digoxin was discontinued and quinidine was again ordered on the 10th hospital day in a dosage of 0.2 gm. every 4 hours; 24 hours later, the temperature began to rise (Fig. 2).

On the 12th hospital day the temperature rose abruptly; after the 8th successive dose of quinidine had been given, it

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reached 103°F. Because the rash that had followed the preceding course suggested hypersensitivity to the drug, and also because the patient only then recalled "ringing in the ears" when he had been given "white pills" for an attack of tachycardia 3 months previously, it was suspected that the fever was also an allergic reaction. The drug was again discontinued after a total of 11 doses (2.2 gm.). However, the temperature continued to rise, reaching a peak of 104.2°F., 20 hours after the last dose of quinidine had been given. The fever then began to subside, and the temperature fell to normal 3 days after the drug had been stopped.

Except for mild diarrhea the patient offered no complaints, and even at the height of the fever the physical findings were unchanged. Laboratory tests were negative, including sedimentation rate, white-cell count, blood culture and tests for febrile and cold agglutinins. Chest x-ray films revealed no pulmonary changes.

On the 18th hospital day there was a febrile episode due to pulmonary embolism, the temperature returning to the normal range after 48 hours and Dicumarol and penicillin having been started.

A single test dose of 0.1 gm. of quinidine sulfate was given on the 24th hospital day. Six hours later the temperature rose sharply and reached 102.6°F. 10 hours after administration. This was accompanied by anorexia, nausea, vomiting and diarrhea. The temperature returned to normal within 24 hours.

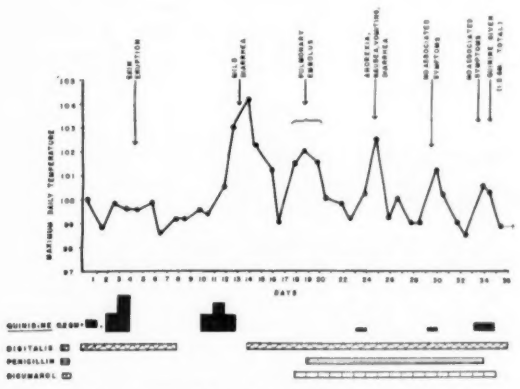

FIGURE 2. *Effect of Quinidine in Case 2.*

The first administration was followed by a transient rash, and the second by high fever. The administration of small test doses on the twenty-third, twenty-ninth and thirty-third hospital days produced prompt febrile reactions. No such reaction occurred after quinine was given on the thirty-fifth day.

Other test doses of 0.1 gm. and 0.2 gm. of quinidine sulfate given on the 30th and 34th hospital days again produced a rise in temperature (to 101.2 and 100.4°F). There were no gastrointestinal symptoms on either of these occasions. The temperature fell rapidly both times. When the febrile reaction to the last test dose of quinidine was beginning to subside, quinine sulfate (in doses of 0.3 gm. every 4 hours, a total of 1.5 gm.) was given to rule out possible cross sensitivity. No reaction took place.

A skin-sensitivity scratch test (method of Boerner) using 0.1 gm. of quinine sulfate, performed on the 26th hospital day, was negative.

CASE 3. B. X., a 52-year-old draftsman with no personal or family history of allergy, was admitted to the hospital on January 15, 1951, suffering from acute myocardial infarction. He was placed on the usual coronary regimen and was given anticoagulant therapy. Because of frequent premature contractions, quinidine was administered in a dosage of 0.2 gm. every 6 hours for 6 days, and every 8 hours on subsequent days. The temperature rose to 102.4°F. in the first 24 hours after admission, returning to normal by the 5th day (Fig. 3). The patient's general condition remained satisfactory thereafter.

On the 14th hospital day the temperature rose abruptly to 103.4°F., and remained between 101 and 102.4°F. during the following days. The patient had no complaints. Examination gave no evidence of extension of the myocardial infarction or of thrombophlebitis with thromboembolic complication. The possibility of respiratory and urinary-tract infections was considered and ruled out. On the 4th day of the febrile episode the patient was still comfortable, and the physical examination was negative except for a flushed face and mild hyperemia and edema of the posterior pharyngeal wall, without evidence of throat infection or adenopathy. Search for a rash disclosed a blotchy macular eruption, which was confined to the back. This had not disturbed the patient. When questioned, he described it as "slightly itchy."

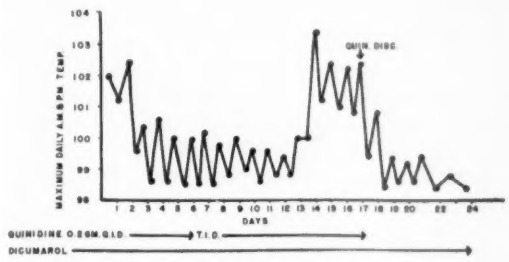

FIGURE 3. *Effect of Quinidine in Case 3.*

The temperature rose on the fourteenth day of quinidine medication. It subsided promptly when the drug was stopped on the seventeenth day.

Quinidine sensitivity was suspected, and the drug discontinued after the morning dose on the 18th hospital day. The temperature was still elevated to 102.4°F. on that afternoon. It then began to fall, becoming normal 36 hours later. The rash subsided and disappeared on the 3d day. The temperature remained normal until discharge.

DISCUSSION

Drug fever, like thrombocytopenic purpura, can be a manifestation of "drug allergy."[7] Also like purpura the fever is one of the rare reactions that may follow quinidine administration. Most of the patients with fever due to quinidine have simultaneously presented other signs or symptoms of allergy. Although the fever appears to be a relatively benign syndrome, recognition is essential, because of possible deleterious effects, particularly when coincident, serious heart disease is present. It is apt to confuse the diagnosis and may lead to unnecessary medication or to treatment that may in itself be harmful to the patient. At the very least, the patient is likely to be subjected to needless diagnostic tests if the origin of the fever is not recognized.

Fever due to quinidine is usually readily identified by one or more of the following criteria.

Quinidine has been administered consistently for ten or more days, or the drug has recently been readministered to a previously sensitized patient.

There is a discrepancy between the relative well-being of the patient and the height of the fever.

The absence of findings characteristic of any recognized febrile pathologic entity.

The concomitant presence of other allergic phenomena, particularly an asymptomatic or slightly pruritic macular rash (eosinophilia is uncommon).

Gradual defervescence over a period of approximately forty-eight hours after quinidine administration has been discontinued.

That cases of quinidine reaction are being increasingly reported may be due to an increase in the use of the drug in a greater variety of arrhythmias. It is emphasized that high fever and other severe reactions have not been sufficiently common to influence the use of this valuable drug when it is indicated. In the rare cases in which such reactions occur, procaine amide[8] or one of the digitalis preparations may be useful substitutes.

Summary

Three additional cases of quinidine drug fever are presented. The importance of recognizing the syndrome is emphasized, and criteria for its identification are enumerated.

We are indebted to Dr. R. C. Schleussner for permission to study Case 2.

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MEDICAL PROGRESS

THE USE OF DIGITALIS IN INFANTS AND CHILDREN*

A Clinical Study of Patients in Congestive Heart Failure

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OVER one hundred and sixty years ago, Withering[1] first described the usefulness of digitalis in the treatment of certain types of "dropsy." About fifteen years later, Ferriar[2] first attributed the efficacy of digitalis to its effect on the heart.

Early in the twentieth century, the principal use of digitalis was found to be in the treatment of auricular fibrillation (Cushny[3] and Lewis.)[4] Within the past twenty-five years, however, digitalis has become the drug of choice in the treatment of congestive heart failure of adults with or without auricular fibrillation (Christian,[5] Luten,[6] Wenckebach[7] and Levine[8]). Digitalizing dosages have been successfully worked out for adults by Eggleston,[9] Gold,[10] De Graff et al.[11] and others.

No such unanimity about digitalis therapy exists in the pediatric literature. Goodman and Gillman,[12] in their textbook of pharmacology, say, "It is usually stated that children require more digitalis per pound than do adults, and that from 50 to 100 per cent more drug than calculated on the basis of body weight must be given to obtain results." Others believe that the difference in effective dosage may not be due to the age or size of the children but rather to "associated factors," such as cardiac reserve, character of disease and degree of failure.[13]

Actually, the number of papers on the use of digitalis in children is scant. McCulloch and Rupe,[14, 15] in 1921 and 1922, described their studies on the effects of digitalis on children with and without heart disease. In 1951 Mathes and his associates[16] reported on the effect of the glycoside on a group of healthy children. Jacobsen and Davison[17] and Schwartz et al.[18-21] reviewed their experience in the treatment of children with rheumatic heart disease in the early 1920's. Walsh and Sprague[22] reviewed the same subject ten years later. Vianello[23] studied the electrocardiograms of a small group of children who received digitalis. Calodney and Carson,[24] in their paper on coarctation of the aorta in infancy, suggest a digitalization schedule for infants.

No detailed reports are available in the literature, however, on the usefulness and dosage of digitalis

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in the varied conditions causing congestive heart failure in children.

In view of the paucity and the conflicting nature of the available information, the present study was planned to clarify the etiology of congestive heart failure in infants and children and to find out how the different etiologic entities respond to digitalis. We also hoped to gather information about the dosage of digitalis, its effect on the electrocardiogram and the dangers of toxicity.

Material and Methods

Forty-one unselected consecutive patients in congestive heart failure were studied. All these children were admitted to the Medical Service of the Children's Medical Center during a two-year period (1950–1951) and were carefully observed by at least one of us. In each case, daily clinical observations were made and recorded on a special sheet. Frequent electrocardiographic tracings were obtained in close temporal relation with the administration of a cardiac glycoside, especially during initial digitalization.

Evidence of right-sided congestive heart failure was shown in all patients by the presence of tachycardia, tachypnea, distention of the jugular vein and hepatomegaly. Peripheral edema was present in only a few cases. In at least half the patients, in addition to right-sided failure, left-sided congestive heart failure was demonstrated by physical and x-ray evidence of pulmonary congestion. That signs of symptoms of severe right-sided failure may mask the presence of left-sided congestion has recently been demonstrated by catheterization data[25]; hence, considerably more than half our patients may have had failure of the left ventricle. Laboratory confirmation of congestive heart failure — that is, increased venous pressure and prolonged circulation time — was obtained whenever possible.

The clinical response to digitalis was termed "good" when all signs of congestion disappeared. It may be pointed out here that weight loss — an extremely useful index of improvement in adults and older children — cannot be used as an indicator of improvement in infants and small children. It may easily be seen that weight losses amounting to 10 per cent of the total body weight — an easily measured amount in an adult — may well fall within the margin of error of the average infant scale and average weighing technic. The clinical response to digitalis was termed "fair" if there was noticeable improvement in the evidence of failure without complete resolution.

The clinical response was considered "poor" if no clear-cut evidence of improvement was obtained with therapy that was considered to be adequate. In this group, it was believed that an adequate trial of digitalis had been given either if toxicity developed or if very large doses (more than 0.004 mg. per pound of body weight a day) were given for periods of a month or more without noticeable clinical effect but with marked electrocardiographic evidence of the effect of digitalis.

Digitalization, whenever compatible with the patient's safety (that is, in the vast majority of cases), was withheld for at least forty-eight hours to provide a control period in which to observe the effects of oxygen, antibiotics and rest. The total digitalizing dose was usually administered within twenty-four to thirty-six hours, in three or four divided doses.

Two preparations of digitalis glycoside were used exclusively in this study. For initial digitalization, the majority of patients received digitoxin (Digitaline Nativelle) intravenously or by mouth. A few patients whose condition was judged to be of "emergency" nature received lanatoside C (Cedilanid) intravenously. For maintenance, digitoxin was used exclusively.

We considered it advisable to restrict ourselves to the use of only one slowly and one rapidly acting drug because of the obvious benefits to be derived from the increased familiarity with only a few preparations. Digitoxin was selected as the slowly acting glycoside because of its almost 100 per cent absorption from the gastrointestinal tract — a characteristic that was especially important with the small total dosages employed. It was believed that the drawbacks of delayed excretion were minimized by the hospitalization and constant, careful observation of the patient. The choice of lanatoside C as the rapidly acting glycoside was based on our previous familiarity with this drug.

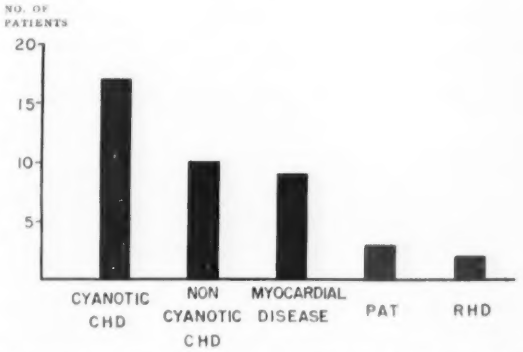

Figure 1. *Diagnoses in 41 Patients Treated with Digitalis. CHD = congenital heart disease; PAT = paroxysmal auricular tachycardia; RHD = rheumatic heart disease.*

Results

Etiology of Congestive Heart Failure

Cyanotic congenital heart disease constituted the largest single group of patients (17), congenital heart disease without arterial unsaturation being represented by 10 cases (Fig. 1). Also included were 3 patients with paroxysmal auricular tachycardia and 2 patients with rheumatic heart disease.

The remaining 9 cases were termed "primary myocardial disease," indicating subendocardial sclerosis or isolated myocarditis.[26]

Age of Patients at Onset of Congestive Heart Failure

The cases were divided into disease groups. Patients with congenital heart disease — cyanotic or noncyanotic — are most likely to manifest cardiac failure within the first six months of life. If they do not do so, they are unlikely to give evidence of failure until two years of age or considerably later. In the patients with paroxysmal tachycardia congestion is also likely to develop in early infancy. In marked contrast to these groups, there was only 1 patient with "myocardial disease" in whom failure appeared under three months of age. The majority did not get into difficulty until over the age of two years. Both patients with rheumatic heart disease and failure were over five years of age.

Clinical Response to Digitalis in Relation to Etiology of Disease

Obviously the groups responding best were the patients with "myocardial disease," paroxysmal tachycardia and rheumatic heart disease (Fig. 2). The validity of this observation in the patients

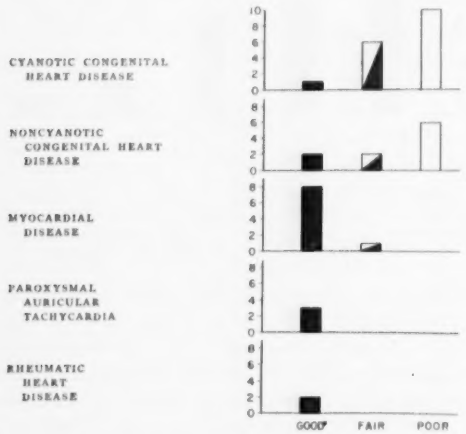

FIGURE 2. *Diagnosis and Clinical Response to Digitalis.*

with rheumatic heart disease is open to question on account of the small number of cases available for study. The cases of "primary myocardial disease" in this study and those of paroxysmal tachycardia in this and another publication[27] represent large enough groups for the observation to be of significance.

In contrast to these groups showing a good response to digitalis were the patients with congenital heart disease, among whom therapeutic failures were numerous. It seems important, however, to emphasize that, although the group as a whole did not respond favorably, a considerable number of "fair" responses and even a few "good" ones were observed in individual cases. The 1 case of cyanotic congenital heart disease exhibiting a "good" response was in a patient with tetralogy of Fallot after a shunt operation.

Digitalis and the Electrocardiogram

The types of electrocardiographic changes seen after digitalization are summarized according to clinical response in Figure 3. It may be seen from this chart that ST-segment, QTc* and T-wave

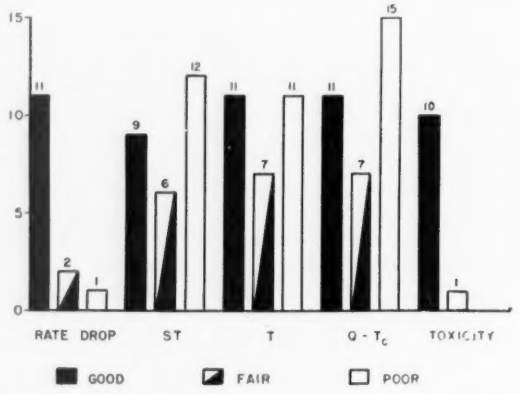

FIGURE 3. *Electrocardiographic Changes in Relation to Clinical Response.*

changes occurred with almost equal frequency in our three groups of clinical response. A significant reduction in rate (more than 40 per minute) accompanied clinical improvement in the majority of the patients with "good" response. Electrocardiographic evidence of toxicity occurred more frequently in cases with "good" than in those with "fair" or "poor" clinical response.

The most consistent electrocardiographic change encountered with what we considered adequate digitalization — irrespective of clinical response — was shortening of the QT_C. All but 8 of the 41 patients showed this phenomenon. The range of this shortening was 0.02 to 0.11 second, with an average of 0.05 second. There seemed to be no correlation between the degree of QT_C shortening and the disease or the dose of digitalis administered.

T-wave changes failed to appear in 12, and the ST segment stayed normal in 14 of the 41 patients. Prolongation of the PR interval was the least sensitive index of digitalization.

By taking frequent electrocardiograms during the period of initial digitalization, we attempted to

*QT_C relates the duration of the QT interval to the cycle length. The formula for QT correction for rate used in this study is that of Bazett[28]:

$$K \text{ or } QT_C = \frac{QT}{\sqrt{\text{cycle length}}}.$$

determine the time sequence of electrocardiographic phenomena after digitalis administration. In the vast majority of cases, digitalis effects were evident in the electrocardiogram within three days of initial digitalis administration. In most cases a clear-cut digitalis effect was present within thirty-six hours. There were only 4 cases in which electrocardiographic changes first appeared beyond the three-day period. (Incidentally, 3 of these 4 patients never showed a clinical response to the drug.)

There was no single electrocardiographic change that tended to appear any earlier than the others. Changes in QT_C, ST segments and T waves occurred with about equal frequency as the first manifestations of digitalis effect. There seemed to be no correlation between disease groups, clinical response, dosage and type of electrocardiographic features to appear first.

Dosage of Digitalis

The dose per pound of body weight was correlated with the clinical response in the 39 cases in which accurate information on dosage was available (Fig. 4). No patient showed a satisfactory response with less than the "average" adult digitalizing dose

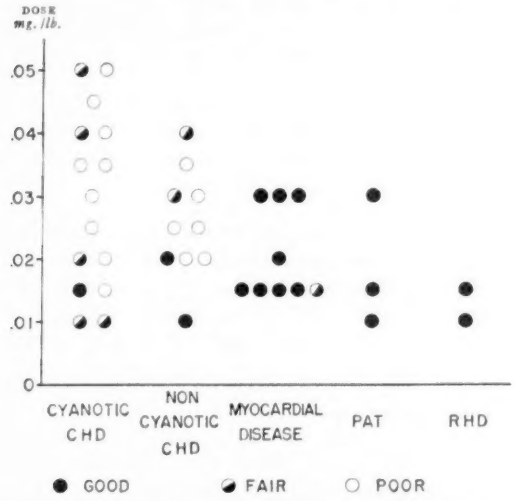

FIGURE 4. *Digitalizing Dose (per Pound of Body Weight) and Clinical Response.*

of 0.01 mg. per pound. It also seems evident from the graph that there were no "good" responses within the group of patients requiring more than 0.03 mg. per pound of body weight for digitalization. Most of the patients who required the high doses either completely failed to show therapeutic effects, or, in a few cases only, their responses could be termed "fair." It seems, then, that the effective digitalizing dose fell between 0.01 and 0.03 mg. per pound of body weight — a wide range indeed.

Following the suggestion of Crawford and his associates,[29] we attempted to correlate the digitalizing dose in milligrams per square meter of surface area with the clinical response (Fig. 5). It seems clear from this graph that the spread of doses associated with a "good" response is fully as wide if calculated by this method as it is if body weight

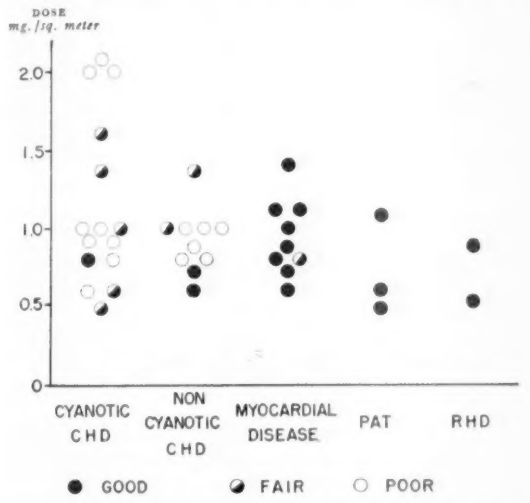

FIGURE 5. *Digitalizing Dose (per Square Meter of Surface Area) and Clinical Response.*

is taken into consideration. The "average" adult digitalizing dose is 0.75 mg. per square meter of surface area. These children needed from 0.5 to 1.25 mg. to achieve optimal clinical response.

The digitalizing dose in milligrams per pound was correlated with the age and clinical response of the patient. All the children two years of age or

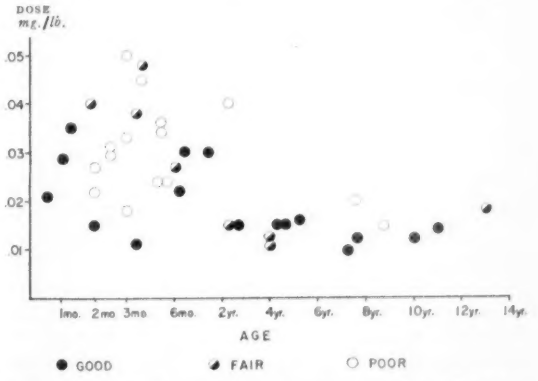

FIGURE 6. *Digitalizing Dose (per Pound of Body Weight) in Relation to Clinical Response and Age.*

older who responded well to digitalis did so with doses of 0.01 to 0.02 mg. per pound of body weight. The majority of the infants under two years of age who showed a satisfactory response required 0.02 to 0.03 mg. per pound of body weight (Fig. 6).

That this correlation between age and digitalis dosage is not due simply to the different types of

heart disease prevalent in the two age groups was demonstrated by correlating digitalis dosage with the disease group and the age of the patient. It became evident that no child over the age of two years required more than 0.02 mg. per pound for successful digitalization, irrespective of the etiology of the disease.

As a daily maintenance dose, a tenth of the digitalizing dose was used in most cases (Taussig).[30] This proved to be entirely satisfactory. No signs of toxicity developed on this regimen, nor did we witness a dissipation of the digitalis effect by clinical or electrocardiographic criteria.

Digitalis Toxicity

Vomiting due to digitalis occurred in 3 cases; all these patients received digitalis in excess of 0.03 mg. per pound of body weight.

There was electrocardiographic evidence of toxicity in a total of 11 patients (Table 1). In none of them was it of serious consequence. Ventricular ectopic beats developed in 3 cases. Four patients showed varying degrees of auriculoventricular block. Four other patients exhibited a changing pattern of the P waves either in a single long tracing or in serial tracings on successive days. In such cases the P wave changed from the normal upright shape to a bifid and then to a diphasic pattern, and finally became inverted. In 2 cases paroxysmal auricular tachycardia, with block, developed. One patient showed sinoauricular block, with nodal escape. There seemed to be no obvious correlation between the appearance of electrocardiographic toxicity and the size of the digitalizing dose. All patients in whom this type of toxicity developed received digitalizing doses ranging from 0.015 to 0.03 mg. per pound of body weight, and the majority of them were in the group receiving 0.015 mg. per pound (Table 1).

TABLE 1. *Electrocardiographic Evidence of Digitalis Toxicity.*

CASE NO.	TYPE OF TOXICITY	DIGITALIZING DOSE *mg./lb. of body wt.*	DIAGNOSIS
10	Ventricular ectopic beat	0.015	Ebstein's disease
12	Changing P waves	0.010	Rheumatic heart disease
16	Auriculoventricular block (1°)	0.010	Rheumatic heart disease
22	Ventricular ectopic beat; auriculoventricular block (1°).	0.029	Primary myocardial disease
28	Ventricular ectopic beat; auriculoventricular block (1°).	0.015	Primary myocardial disease
32	Paroxysmal auricular tachycardia, with block	0.015	Primary myocardial disease
33	Changing P waves	0.018	Primary myocardial disease
34	Paroxysmal auricular tachycardia, with block; changing P waves.	0.015	Primary myocardial disease
38	Auriculoventricular block (complete)	0.027	Primary myocardial disease
39	Changing P waves	0.016	Primary myocardial disease
40	Sinoauricular block, with nodal escape	0.015	Paroxysmal auricular tachycardia

There was, however, a striking concentration of the patients with electrocardiographic evidence of toxicity within the disease groups affecting the myocardium (Table 1). Seven of the 11 cases were classified as primary myocardial disease, and 2 as rheumatic pancarditis. One patient was proved to have Ebstein's disease, a condition well known for the frequency with which arrhythmias develop; a final patient had paroxysmal tachycardia.

DISCUSSION

The case material reflects the incidence of conditions causing congestive heart failure in this institution. The number of patients with rheumatic heart disease is small (2 of the 41) because the majority are admitted to the House of the Good Samaritan for treatment. There are no comparable figures available in the pediatric literature on the etiology of heart failure that is nonrheumatic in origin.

The large number of patients with congenital heart disease is not surprising in view of the increased attention being paid to this condition within the past decade. The number of cases classified as "primary myocardial disease" was unexpectedly large and prompted us to review this group in a separate publication.[26] Three patients with paroxysmal auricular tachycardia within a two-year period represent, we believe, the average frequency of this condition in a large pediatric center. We cannot account for the fact — except by the stringent criteria for a diagnosis of congestive heart failure — that acute glomerulonephritis was not represented in this group. That decompensation caused by cor pulmonale is very uncommon in pediatrics has been pointed out elsewhere.[31]

The large number of patients with congenital and the small number with rheumatic heart disease explain the fact that slightly more than half our patients (23 out of 41) were under seven months of age.

Marvin,[32] in 1926, correlated the effect of digitalis in heart failure with an etiologic classification of the disease in adults. He compared small groups of patients and found that arteriosclerotic heart disease responded best, and rheumatic heart disease least well, to digitalis therapy. He believed that one of the reasons for this discrepancy may be that heart failure in rheumatic fever represents a later stage of heart involvement than failure in arteriosclerosis.

Gold and De Graff[33] maintain that "Digitalis produces most striking therapeutic effects in congestive heart failure in the absence of active infection of the heart." Luten,[13] in his monograph on digitalis, says "The therapeutic response varies in general with the etiologic type of heart disease responsible for the failure." He mentions coronary-artery disease as especially prone to show good response, and rheumatic and syphilitic disease and primary myocardial conditions as less likely to be responsive.

The same author believes, as Gold and De Graff do, that the presence or absence of infection may prove to be the chief differentiating factor between the groups responding well and poorly.

Discussing digitalis in relation to rheumatic carditis in children, Schwartz and Levy[21] and Taran[34] regard the drug as dangerous and rarely, if at all, helpful. Walsh and Sprague[22] and Ash,[35] in equally well documented studies, found the glycoside useful in a large percentage of their patients with rheumatic heart disease.

The use of digitalis in cardiac failure of patients with congenital heart disease is discussed by Taussig[30] in her monograph and by Gibson.[36] Both authors believe that in selected cases the glycoside may be used profitably.

There seems to be no adequate study in the literature on the responsiveness of cases of isolated myocarditis and subendocardial sclerosis to digitalis.

The good response of patients with paroxysmal auricular tachycardia to digitalis has been pointed out repeatedly.

Reviewing our data with this body of information as a background, we were surprised to find how frequently cases of mechanical failure caused by congenital heart disease failed to respond. In view of the discouraging opinions expressed by a number of authors regarding the benefits of digitalis therapy to be expected in rheumatic fever or other types of myocarditis, we were equally surprised to observe the excellent results obtained in our patients with myocardial disease.

The poor response of patients with pure right-sided heart failure — that is, cor pulmonale — to digitalis is a well documented fact. It is also generally accepted that patients whose congestive heart failure is primarily of the left-ventricle type respond well to digitalis. It is possible that the difference in the response to digitalis between our etiologic groups is at least partially based on the type of failure. Although all patients gave evidence of some right-sided failure, it may safely be assumed — on the basis of physiologic and pathological studies — that in most patients with congenital heart disease the failure is almost exclusively right sided. In contrast, the patients with primary myocardial disease, rheumatic heart disease and paroxysmal auricular tachycardia all show significant involvement of the left ventricle, physiologically as well as pathologically. It has previously been pointed out that the failure of the left ventricle may well be masked clinically by the coexisting or secondary right-sided congestion. It is interesting to note, in this respect, the very favorable effect of digitalis on the congestive heart failure of infants with uncomplicated coarctation of the aorta, a disease involving considerable failure of the left ventricle.

It may also be significant that the only cyanotic patient who responded well to digitalis was a little girl with tetralogy of Fallot in the postoperative period of a Potts procedure. This is a situation in which the shunt operation added the left-ventricle-flow work to the considerable right-ventricle-pressure work that had existed for many years. It seems reasonable to assume that the success of digitalis in this case was due to its effect on the failing left ventricle.

It is quite striking that the patients with myocardial disease — rheumatic or nonrheumatic — who responded optimally to digitalis were the same ones who gave electrocardiographic evidence of toxicity on relatively low dosage. This is in marked contrast to the group of patients with congenital heart disease, who did not have signs of toxicity by electrocardiogram but who also failed to derive any benefits from huge doses of the drug. We can thus confirm the findings of a number of authors who have described how frequently digitalis intoxication occurs in myocardial diseases, but in contradiction to the opinion of these authors, we have found that these are the same patients who respond best to the cautious administration of the glycoside. We thus regard both toxicity and therapeutic effects as expressions of sensitivity to digitalis. A number of recent experimental observations on the biochemical patterns of the myocardium tend to support this clinical finding.[37]

Quite often the optimal therapeutic dose was within the range of electrocardiographic toxicity; in other cases, by diminishing the dose slightly, we were able to achieve maximal therapeutic effect without any evidence of intoxication.

It must be emphasized that these conclusions are based mainly on observations of patients with "primary myocardial disease" (subendocardial sclerosis and isolated myocarditis), only a few patients with rheumatic heart disease and none with diphtheria being included.

Serum potassium levels were determined in 9 of our 11 patients with toxicity and were found to be within normal limits in all. This does not obviate the possibility that the electrocardiographic abnormalities were based on changes in the intracellular potassium level, as suggested by Lown et al.[38]

One other aspect of digitalis intoxication may be mentioned: the relative infrequency of ventricular ectopic beats as evidence of intoxication and the rather common occurrence of auriculoventricular-conduction disturbances and auricular arrhythmias. This experience is quite different from the findings in adults.

Our electrocardiographic findings — short of toxicity — after administration of digitalis were in agreement with those of others.[39, 40] No single electrocardiographic phenomenon, nor any combination of phenomena, could replace good clinical judgment in determining a satisfactory level of digitalization. No single electrocardiographic feature always appeared first in our series. Shortening of the QT_c was the most consistent digitalis effect in the elec-

trocardiogram. A lengthening of the PR interval was the least likely to occur with the dosages employed. In contrast to the observations of Schwartz and Levy,[21] sinus slowing was more likely to accompany therapeutic success than failure.

A great deal of controversy surrounds the dosage of digitalis to be used in pediatrics. Eggleston[9] observed that age did not influence the dosage of the glycoside per pound of body weight. Walsh and Sprague[22] successfully used adult dosage in rheumatic children. Mathes and his associates,[16] studying the electrocardiograms of normal children, found their sensitivity not significantly different from that of adults.

McCulloch and Rupe[15] reported that children required between 50 and 100 per cent more digitalis per pound of body weight than adults. Jacobsen and Davison[17] found, in 26 patients with rheumatic heart disease, "that even larger doses are beneficial." Crawford et al.[29] believe that the higher dosages required by the young correspond to their relatively larger body-surface area.

Our observations indicate that the younger the child, the more digitalis per pound or per square meter of surface area is required, irrespective of the disease causing the congestive heart failure. Young infants may require as much as 0.03 mg. of digitoxin per pound of body weight, whereas older children may respond favorably to amounts no larger than the adult "average" digitalizing dose of 0.01 mg. per pound. Animal experiments, revealing significant differences in potassium content and in creatin-phosphocreatin ratio between the hearts of younger and older animals, may serve as an explanation for this difference in sensitivity between age groups.[41, 42] A reasonable dosage schedule has evolved from our data, on the basis of age and weight.

It must be emphasized, however, that any dosage schedule such as this should only serve as a guide. Every patient's digitalization should be conducted as an individual experiment within the calculated dosage range.

Summary and Conclusions

The response to digitalis of 41 infants and children in congestive heart failure is described.

The incidence of nonrheumatic causes of congestive failure in the young is discussed. Congenital heart disease and "primary myocardial disease" are the two most common conditions encountered in this group.

Congenital heart disease and paroxysmal tachycardia are most likely to cause failure within the first six months of life. Patients with myocardial disease and rheumatic fever are most likely to fail after two years of age.

The most satisfactory response to digitalis was obtained in patients with myocardial disease, paroxysmal tachycardia and rheumatic carditis. The least satisfactory results were obtained in children with congenital heart disease, especially those with cyanosis.

No accurate estimates of the level of digitalization could be obtained by the electrocardiogram. The most consistent electrocardiographic change following digitalis administration was shortening of the QT_C.

A satisfactory dosage schedule may be obtained if the age and weight of the patients are taken into consideration. Patients under two years of age need 0.02 to 0.03 mg. of digitoxin per pound of body weight for digitalization. Children over two years respond favorably to dosages ranging between 0.01 and 0.02 mg. per pound of body weight.

Electrocardiographic evidence of digitalis intoxication was found most commonly in the patients who responded most favorably to the glycoside.

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MEDICAL INTELLIGENCE

TWIN PREGNANCY RESULTING IN THE BIRTH OF A VIABLE INFANT AND A BLIGHTED FETUS

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LYNN, MASSACHUSETTS

THE possibility of the birth of a viable infant at or near term accompanied by a blighted twin fetus delivered before the seventh month of gestation has been known for many years. Reference to such occurrences has been made in many of the older handbooks of midwifery, such as those of Guilleneau (1594), Peu (1694), Mauriceau (1695), Chapman (1735), Burton (1751), Smellie (1752), Albert Haller (*Elements of Physiology*, 1780), and Krause (1853). Ramsbotham states that this condition was remarked upon by Pliny. Despite the availability of this knowledge, many references to such occurrences during the last century are in the form of letters to the editors of medical journals briefly reporting such cases and asking for information concerning them. Supoux was probably the first to examine the necrotic placenta under the microscope and report his findings.

The present paper is a brief description of such a case, with delivery on January 6, 1946.

CASE REPORT

A. M., a 39-year-old gravida VI, was admitted to the Lynn Hospital at full term. All previous pregnancies and deliveries had been uneventful, and her children were all living and well. At the beginning of the 5th month of gestation, she started to bleed, passing clots but never experiencing pains or contractions in the lower abdomen. This hemorrhage continued for 4 or 5 days and then cleared. During the remainder of pregnancy, she continued to have occasional staining, edema of the ankles and frontal headaches.

The first stage of labor began at 8:40 p.m. and the third stage ended at 10:31 p.m., when she was delivered of a normal, living, 6-pound female infant. When expression of the placenta was attempted, a bony structure was felt, and shortly thereafter a fetus (consistent with a 5-month pregnancy) was delivered. Its placenta was 1 handbreadth in size. The fetus was not decomposed; it was red, the head was compressed; there was no odor. The fetus and the full-term baby were in separate amniotic sacs.

The pathological report was as follows:

> Examination shows a placenta that is partially degenerated. It is complete with membranes and a segment of umbilical cord 30 cm. in length. The placenta appears to be partially torn at one edge, although the cotyledons seem to be present and intact. The placenta measures approximately 15 cm. in diameter. Multiple sections reveal a yellowish to reddish color. There are several areas of infarction necrosis. The tissue is poorly preserved. The placenta appears to be divided into 2 unequal portions by a septal membrane, which is almost completely torn away. The smaller of the two halves is almost completely infarcted. The larger half, to which the healthy cord is attached, is well preserved.

The final diagnosis was twin placenta with infarction necrosis of one half and with no evidence of cancer or of hydatid-mole formation.

The normal infant delivered at that time is at present living and healthy.

APPARATUS FOR CONTINUOUS BLOOD-PRESSURE OBSERVATION

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CAMBRIDGE, MASSACHUSETTS, AND WASHINGTON, D.C.

IN the course of a series of investigations concerning human cerebral hemodynamics a relatively inexpensive, compact apparatus was improvised for continuous observation of the mean arterial blood pressure. Although we had considered the instrument assembly to be of chief worth in experimental studies, the lack of necessity for further mechanical refinement made it evident that there might be considerable clinical application. In particular, immediate detection of

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blood-pressure changes is of inestimable value in anesthesiology, in certain diagnostic procedures (for example, to detect pheochromocytoma) and in initial therapeutic trials of the more dramatic hypotensive agents, as in eclampsia or hypertensive crises.

Description

The aneroid manometer is removed from an ordinary blood-pressure cuff and a 1.3-cm. length of 0.8-cm. gum-rubber tubing, such as that used for intravenous infusions, is slipped over the hose nipple of the manometer as a bushing. The open end of a 2-cc. lock-tip syringe barrel is forced over

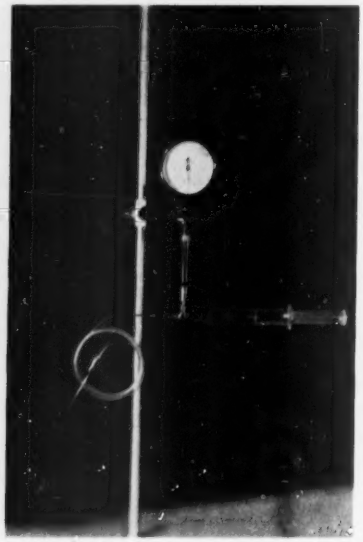

Figure 1. *Assembled Apparatus for Continuous Blood-Pressure Observation.*

the bushing, which may be moistened slightly for ease in assembling, and the side arm of a three-way stopcock is attached to the tip of the syringe barrel. A convenient length of polyethylene catheter or other small-bore flexible tubing is attached to the stopcock outlet by means of a Tuohy adapter, cut-off hypodermic needle of proper gauge or other suitable fitting. A 5-cc. or 10-cc. lock-tip syringe filled with 5 per cent sodium citrate solution or with heparinized saline solution (2 mg. per cubic centimeter of heparin) is attached to the stopcock inlet. The indwelling arterial needle may be attached to the free end of the tubing by means of a variety of male (preferably lock-tip) adapters; if these are not commercially available for the size of tubing used, one may make them by soldering lengths of hypodermic-needle tubing into the shanks of cut-off "tonsil extensions," or needles may be combined with discarded metal tips of broken lock-type syringes (Fig. 1) by filing and soldering.

Method of Use

The assembly, sterile except for the manometer and bushing, is hung or clamped (a laboratory burette clamp is most convenient) in a vertical position on a suitable stand (Fig. 1) with the center of the small syringe barrel at the approximate level of the artery to be used. The polyethylene catheter should be long enough to reach from this artery to the observer's position with sufficient excess not to stretch across empty space and to be tucked or taped under available protective overhang.

The stopcock-valve handle is turned to the sidearm, and the 2-cc. syringe barrel ("pressure chamber") is filled slowly from the large syringe ("reservoir") until the manometer registers a level somewhat higher than the anticipated mean arterial blood pressure. Rapid or jerky filling must be avoided since it may cause fluid to spurt up into the manometer bellows, with possible corrosion and damage, as well as contamination of the contents of the pressure chamber. The stopcock-valve lever is next turned to the inlet arm, and air in the tubing is displaced by fluid from the reservoir syringe, the plunger of which should move freely. Arterial puncture is performed with the needle attached to the distal end of the transparent tubing, and as soon as the vessel is entered, as indicated by the reflux of blood, the stopcock is quickly turned down, away from the side arm. The compressed air within the manometer and pressure chamber will now force fluid from the chamber into the tubing and thence into the artery, until pressure equilibrium is reached. Pulsations of the manometer needle can be damped out until barely discernible, but no further, by slow turning back of the stopcock valve.

When the blood pressure shows progressive elevation during use of the apparatus it is advisable to flush out the tubing and needle with a small quantity (depending chiefly on the amount of reflux of blood) of anticoagulant fluid at ten-minute intervals; if the pressure is fairly constant this attention may be required only after periods of fifteen or twenty minutes; with progressive blood-pressure reduction no manual clearing of the apparatus is necessary, and full attention can be devoted to whatever clinical problems may be present.

Advantages

Although most of the advantages of this apparatus assembly are self-evident, they may be listed briefly. In the first place, operation is continuous and automatic, permitting observation of the blood pressure at a glance and at any time. Secondly, maintenance of operation requires little attention,

which may usually be deferred until convenient. Thirdly, the apparatus is simply contrived of parts everywhere obtainable and is compact and easily manipulated and sterilized. (The manometer and rubber bushing, of course, do not require sterilization and must not be subjected to the procedure.) Finally, when lock-tip attachments are used the assembly is not subject to breakage; the flexibility of the rubber bushing connection, which must be tight enough to prevent leakage or slipping, augments this feature.

Disadvantages and Precautions

The chief disadvantage of the method is that arterial puncture is required, and, depending on the artery selected, if the needle becomes occluded or carelessly dislodged, it may not easily be replaced. One may avoid displacement by taping over the indwelling needle a 7.6-cm. transparent plastic hemisphere, its edge deeply notched for egress of the tubing; an ideal protective cover of this description may be made from part of a child's rattle. Although a minute clot within the needle can often be dislodged by manual pressure from the reservoir syringe, this may not be possible, and, in any case, such a clot is likely to re-form. Such clotting has seldom occurred, in our experience; nevertheless, if the needle cannot be replaced or if any other accident renders the apparatus non-operative, it is mandatory that a conventional sphygmomanometer be at hand, preferably already applied.

The femoral artery appears not to be subject to thrombosis at the site of an indwelling needle left in place for relatively short intervals; moreover, we have rarely encountered appreciable bleeding after withdrawal of an 18-gauge needle and never, in several hundred cases, after removing a 20-gauge needle. It should be noted that in our studies we invariably used heparin as an anticoagulant. Nevertheless, except for possibly increased liability to clotting, we are inclined to recommend use of short-bevel 21-gauge or 22-gauge arterial needles. The more important difficulties associated with selection of the femoral artery are that at surgical operation the area becomes inaccessible after draping, several feet of polyethylene catheter are needed to reach an observation post at the head of the table, and puncture may be difficult, at least requiring a long needle, in obese patients. Most of these objections may be overcome by the selection of the brachial artery at the elbow, but the possibility of thrombosis, however low the probability, must be considered. We hesitate to recommend use of the common carotid artery for the same reason.

The possibilities of introducing air or bacteria into the blood stream deserve comment. As indicated above, care in the initial filling of the pressure chamber will prevent contamination of the fluid, and the arterial pressure never goes high enough, barring leakage of air, to force the anticoagulant fluid into the manometer. Conversely, if the arterial pressure were to fall to atmospheric levels the total volume of compressed air would not be great enough to cause it to enter the tubing.

Summary

A compact, easily assembled apparatus for continuous observation of mean arterial blood pressure, of value in assessment of acute peripheral circulatory changes, is described. Advantages and disadvantages associated with such a direct means of blood-pressure measurement are listed and discussed.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39031

PRESENTATION OF CASE

A fifty-six-year-old bartender was admitted to the hospital complaining of chest pain of two weeks' duration.

The present illness began four weeks before admission with awareness of mild dyspnea, especially on exertion or on bending over. He continued to sleep on one pillow. Two weeks later a "cold," tightness of the chest, and cough productive of thick, white sputum developed, being followed in a few days by the onset of sharp, "razorlike" substernal pain accentuated by coughing or deep breathing. Two days later the pain spread to the left shoulder and left costal margin. A week before admission a physician had given him an injection of penicillin, aureomycin, four times daily for three days, and then another penicillin injection. The family believed that he had improved with this treatment, but the patient thought he had changed very little. In the last few days before admission the pain and dyspnea had become more severe. He was definitely more comfortable sitting up. He denied hemoptysis, ankle edema, abdominal pain, tarry stools, chills or fever. He thought he had gained a little weight. He had continued to be constipated off and on. He had drunk small quantities of alcohol daily for a long time but claimed to have had a good diet.

The patient had mild diabetes for the past eight years, controlled with 30 units of insulin daily until eight months previously, when he stopped using it because the urine reaction was always blue. During this eight-year period he was seen in the Out-Patient Department on several occasions for treatment of infected abrasions, and sixteen months before this entry he was admitted for treatment of cellulitis of the left heel. At this time because of an incidental history of slight weight loss, increasing constipation and tenesmus over a six-month period, with occasional bilateral low abdominal pain, a barium-enema examination was done. This showed changes suggesting a filling defect at the right end of the transverse colon. Sigmoidoscopic examination was negative. A fasting blood sugar was 257 mg. per 100 cc. He was discharged after three days and referred to the Diabetic Out-Patient Clinic. A repeat barium-enema examination two weeks later confirmed the presence of a grossly irregular mucosal pattern suggestive of ulceration in the hepatic flexure for a distance of 5 cm. This irregularity was associated with a demonstrable shelf, which was more prominent on the inferior aspect. The stool guaiac reaction was negative. The patient was given an appointment for admission to the hospital for exploratory laparotomy but was not seen again until the final admission fifteen months later.

Physical examination showed a well developed and well nourished man with a rather flushed face and in no apparent distress. When he was flat in bed the head, neck and upper part of the chest became very congested and the ear lobes cyanotic. There was nonpulsatile distention of the neck veins. The trachea was in the midline. The anteroposterior diameter of the chest was increased, with diminished excursions. There were dullness and diminution of breath sounds at both bases, more marked on the right. The breath sounds in the upper part of the chest were bronchovesicular. The anterior mediastinum on percussion was 11 cm. in width. There was no d'Espine, Broadbent or Ewart sign. The left border of cardiac dullness was in the anterior axillary line in the sixth intercostal space. The heart sounds were distant, with a regular rate. At the left of the sternum in the third intercostal space there was a scratchy systolic bruit. The aortic second sound equaled the pulmonic. There was a 15-mm. pulsus paradoxus. The upper border of the liver was in the fourth intercostal space. The lower edge was tender, and palpable 3 fingerbreadths below the right costal margin. There was no clubbing of the fingers or peripheral edema.

The temperature was 102°F., the pulse 110, and the respirations 24. The blood pressure was 110 systolic, 85 diastolic.

The urine was yellow, acid and of insufficient quantity for specific-gravity determination, and gave a ++ reaction for albumin and a green reaction for sugar; the sediment contained 2 to 5 white cells and an occasional granular cast per high-power field. The blood hemoglobin was 14 gm. per 100 cc.. and the white-cell count 18,100, with 75 per cent neutrophils and 25 per cent lymphocytes. The alkaline phosphatase was 7.1 units, the nonprotein nitrogen 45 mg., and the total protein 6.62 gm. per 100 cc., with an albumin-globulin ratio of 2.5. The prothrombin time was 16 seconds (normal, 13 seconds) and the cephalin flocculation was ++ in twenty-four and forty-eight hours. A bromsulfalein test showed 30 per cent retention of the

dye. A finger stool specimen gave a + guaiac reaction. Skin tests with old tuberculin 1:100,000 and 1:1000 were negative. A sputum smear was negative for acid-fast bacilli; a culture grew out Type D pneumococci. Venous pressure was equivalent to 200 mm. of saline solution in the left arm and 160 mm. in the left leg. The circulation time with 5 cc. of Decholin was 15 seconds, arm to tongue, with a good end point, and 60 seconds, leg to tongue, with a poor end point. An electrocardiogram revealed sinus tachycardia at a rate of 110, a PR interval of 0.12 second and a QRS interval of 0.08 second, with normal voltage and axis. The ST segment was slightly elevated, with low upright T waves in Leads 1, 2, AVL, AVF, V_4, V_5 and V_6. There was depression of the ST segment in Lead AVR, and flat or low-upright T waves in Leads V_1, V_2 and V_3. A small Q wave was present in Leads 1, 2, 3, AVL, AVF, V_4, V_5 and V_6. A roentgenogram

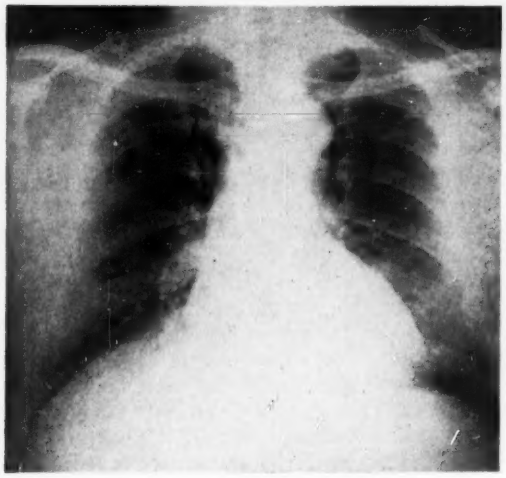

FIGURE 1. *Roentgenogram of Chest Taken Nine Years before Admission.*

of the chest showed the heart size to be increased since the previous examination nine years before admission, but the shape did not suggest pericardial effusion (Fig. 1 and 2). There was fluid in the right pleural cavity and a shadow at the right base suggestive of atelectasis. There was no evidence of metastatic disease in the lungs. A plain film of the abdomen demonstrated some liver enlargement. On the following day fluoroscopic examination of the chest was reported as showing pericardial effusion.

The patient was digitalized and given a low-salt diabetic diet. On the third day a right thoracentesis was done, and 75 cc. of thin, amber, slightly blood-tinged fluid, which contained 120 white cells and 10,000 red cells per cubic millimeter, as well as many bacteria, was removed. Venous-pressure determination was equivalent to 208 mm. of saline solution. A repeat chest roentgenogram showed no change.

On the third hospital day the venous pressure was equivalent to 210 mm. of saline solution. The patient seemed more dyspneic. The blood pressure was 110 systolic, 80 diastolic. The temperature was 101°F., the pulse 100, with many ventricular premature beats, and the respirations 40. The white-cell count was 22,000.

On the fourth hospital day the pulse had increased to 110 to 120; the blood pressure was 100 systolic, 85 to 90 diastolic. The dyspnea had in-

FIGURE 2. *Roentgenogram of Chest Taken on Admission.*

creased, and the heart sounds were more distant. On pericardial tap performed below the xiphoid process 3 cc. of yellow, grossly purulent fluid was recovered. There was no improvement clinically, and later the same day a second pericardial aspiration was performed in the operating room. The needle was inserted in the third intercostal space 2.5 cm. to the left of the sternum, and 350 cc. of orange-brown fluid was withdrawn. Examination of the fluid was negative for acid-fast bacilli. It contained many red cells and neutrophils and a few lymphocytes. There were many gram-positive diplococci and a few staphylococci and streptococci. After this procedure, the patient was more comfortable. A culture was subsequently reported as positive for Type D pneumococci. The blood pressure was 120 systolic, 90 diastolic, the pulse 100, the respirations 24, and the temperature 99.4°F. by rectum. However, one and a half hours later the blood pressure rose to 190 systolic, 130 diastolic, the pulse became faint, the respirations increased to 40, and the patient became cyanotic. A precordial friction rub was heard. Subcutaneous

emphysema of the anterior chest wall was apparent. He was placed in an oxygen tent and given morphine, penicillin, 300,000 units intramuscularly four times daily, and streptomycin, 0.5 gm. intramuscularly every eight hours. Three hours later the pulse was 144, the respirations 40, and the blood pressure 100 systolic, 80 diastolic. Vascular collapse occurred, and the heart sounds became inaudible. A third pericardial tap was done through the third left intercostal space, and 100 cc. of yellow-brown fluid was removed, without improvement in the clinical picture.

On the evening of the fifth hospital day the blood pressure was 140 systolic, 100 diastolic, the heart rate 120, and the respirations 30. The patient was breathing noisily, with shallow respiration, and was unresponsive except for sluggish reaction to pain. The pupils were constricted and fixed. There was an extensor plantar reflex on the right and bilateral ankle clonus. The knee, ankle, biceps and triceps deep-tendon reflexes could not be obtained. Immediately after completion of a neurologic examination he was found pulseless. Artificial respiration and cardiac stimulations were tried without success.

Differential Diagnosis

Dr. Edward F. Bland: It seems obvious that we are dealing here with pericardial disease, cardiac tamponade and infected fluid. We shall have to decide whether or not the purulent fluid was the primary or the secondary cause of this illness and death.

From the history the course seems to have been subacute; it does not sound quite hectic enough for a purulent pericarditis. The patient was ill for four or five weeks, but the course was not too febrile and did not give cause for alarm until near the end. Also, the history suggests obstruction of the circulation; if the single observation of nonpulsatile distended neck veins is correct, that too means obstruction outside the heart. In most patients with cardiac tamponade the veins pulsate, even with chronic constrictive pericarditis. Yet, of course, if the venous pressure was so high that the veins were completely filled, perhaps pulsation could not be easily seen. The fact that he became cyanotic when he assumed the recumbent position is compatible with superior mediastinal obstruction, but since the liver was distended too, the obstruction also included the inferior vena cava. I think the evidence is quite good that the pericardium was involved no matter what process may have been present in the mediastinum. The electrocardiogram supports that somewhat.

There are a few points that are not quite so clear. There is one bit of important information that I am sure must be in the record. The chest was tapped once, and the pericardium was tapped three times; someone must have examined those fluids under the microscope for tumor cells, but no mention is made of it.

Dr. Stuart Ragland, Jr.: The pleural fluid was looked at under the microscope by the house staff, and finally by Dr. Castleman. Some cells were atypical, but Dr. Castleman believed that was not enough on which to make a diagnosis of cancer.

Dr. Bland: What about the pericardial fluid?

Dr. Kurt J. Isselbacher: The pericardial fluid was extremely thick and viscid and was obviously pus; microscopical examination revealed abundant neutrophils. Although the color of the fluid from the first tap differed from that of the second, — the first was yellow and the successive tap was brown, — the microscopical examination was the same.

Dr. Bland: Apparently no tumor cells were demonstrated in the pericardial fluid.

Let's ask Dr. Wyman to show the x-ray films.

Dr. Stanley M. Wyman: This old chest film taken about nine years before the last entry (Fig. 1), compared with the one mentioned in the protocol taken fifteen months before the final entry, demonstrates very little change. The lung shadows seem grossly clear on both. The heart shadow is moderately enlarged in the region of the left ventricle, and the aorta is quite tortuous on both these examinations. One film from the barium-enema examinations on two separate days shows a definite mass in the proximal portion of the transverse colon that is seen on repeated films; it seems to be a real and constant finding, with irregularity of the mucosa and apparently with nodularity of the mass.

Dr. Bland: Can you see the liver and spleen?

Dr. Wyman: The spleen does not seem enlarged. The liver does not appear to be appreciably enlarged. In the next film of the chest taken on the final admission the shadow of the heart has increased considerably in diameter (Fig. 2). The statement that it does not have the appearance of pericardial effusion is misleading, because pericardial effusion may look like cardiac enlargement. I do not think there is a characteristic appearance in many cases. The liver is quite well seen, and as nearly as I can compare the liver with its shadow in the previous film, which was taken in a somewhat different fashion, it may have become slightly larger, but this is not very striking.

Dr. Bland: Is the mediastinum any wider?

Dr. Wyman: No, there is certainly nothing very remarkable.

Dr. Bland: The pericardium is not fuzzy.

Dr. Wyman: I do not see any nodules in the heart-shadow outline. I do not see any obviously enlarged lymph nodes. In the more heavily penetrated film I am unable to outline any real masses in the mediastinum. The fluid in the pleural spaces and the enlargement of the pericardial or heart shadow are again seen.

Dr. Bland: Would you say that the patient had cancer of the colon?

*Physician, Massachusetts General Hospital.

DR. WYMAN: I think he did have cancer of the colon; it would be extremely hard to explain the deformity in the colon on any other basis.

DR. BLAND: He had fluid in both lung bases?

DR. WYMAN: Yes; but more on the right.

DR. BLAND: He had no cancer in the chest that you can find?

DR. WYMAN: I do not see any positive evidence for a primary tumor in the lungs.

DR. BLAND: He must have had a malignant lesion beginning in the colon.

Could this have been tuberculosis of the pericardium? The course was not quite like the usual fatal tuberculosis of the pericardium. The patient did not live long enough for the general run of such patients; he grew worse too fast. Sometimes it is difficult to make a diagnosis of tuberculosis of the pericardium. I think it is a possibility here but probably not the most likely one.

The other condition that could do this to the heart or rather pericardium is infection. If this was primarily purulent infection, I have to explain how it reached the pericardium. The organisms could have been introduced directly, but infection was present at the first tap. The patient had had some skin lesions in the past, but they were healed and there was no reason to suspect that he had sepsis or septicemia, which may produce pericarditis. There is no clear evidence of infection anywhere near the heart, in the lung or mediastinum, so I have to decide about the origin of the purulent material that was obtained on the single tap at the xiphoid process but not on the second further up, although the cultures on both were positive for the pneumococcus, Type D. Nevertheless, purulent pericarditis does not appeal to me as the most likely cause of this patient's fatal illness.

I am inclined to think that he had involvement of the pericardium from metastatic carcinoma and although metastasis to the pericardium is not common — we see it perhaps two or three times a year — it is far more frequent than primary tumor of the pericardium or heart. Lymphoma can involve the pericardium too, but there is no clear evidence of lymphoma. In the first place this patient had extreme cardiac tamponade, without much fluid in the pericardium, which means either that this came very quickly (which apparently did not happen here) or that the pericardium was already rigid from inherent disease so that a small amount of fluid within the pericardium might cause a great deal of tamponade.

I do not quite understand, although it probably was apparent to those who were in charge of the patient, what occurred in the operating room. Another tap was done, and this time the character of the fluid was somewhat different. At that point there were three choices: to do nothing further (which apparently was the course adopted); to consider surgical drainage of the pericardium followed by antibiotic therapy; or, if one was convinced that this was not pus or infected pericardial fluid, a pericardial window would have permitted the relief from recurring pressure around the heart. It is not clear from the record what happened at this point except that the patient became progressively worse and died the next day.

Furthermore, I cannot explain the brief episodes — one or two hours — of extreme hypertension in a patient whose cardiac output was seriously impaired by mechanical tamponade. I cannot quite explain the variable microscopical findings in the pericardial fluid, which at least was of a color (sanguineous) to make one suspect cancer.

In conclusion, in spite of the evidence of sepsis at the end, I am inclined to think this patient's primary trouble was metastatic carcinoma of the pericardium.

DR. THOMAS PAINE: You might like to know that the finding of staphylococcus and streptococcus in the pericardial fluid was based on the microscopical examination of a stained smear and not on culture. I think in the culture of the sputum there were numerous colonies of pneumococcus and the pericardial fluid contained only pneumococci on culture. I doubt that there were really two organisms present in the pericardial fluid.

DR. CONGER WILLIAMS: When I saw this patient immediately before the tap was performed in the operating room, it was apparent that he had an advanced pericardial tamponade that needed immediate attention. On tap, 400 cc. of fluid was removed, and the patient became much better at once. Since he had been so sick that day, and at that time we were not absolutely sure of the nature of the fluid, although we suspected it might be purulent, we decided that we should let him alone for the time being. I think one should emphasize also the dramatic character of the dyspnea, which followed the tap by perhaps an hour. When we saw the patient again it seemed to me that he had an extremely difficult, grunting, forced expiration, which one sees with positive-pressure pneumothorax or in air embolism. Against air embolism was the fact that this had occurred so long after the tap. During the tap, air was introduced into the pericardial cavity as is usually done to permit a better visualization of the pericardial structure itself. The patient obviously did not have a positive-pressure pneumothorax in the x-ray films as we feared. We did not explain the terminal event until later.

DR. BLAND: Do we have the films showing air in the pericardium?

DR. WILLIAMS: The films were taken to explain the dyspnea, not to show the air; the patient was far too sick at that time.

DR. WYMAN: Is this the film?

DR. RAGLAND: This is the film that was taken with the air under the sternum.

DR. BLAND: There is some subcutaneously. Perhaps it also went to the brain.

DR. WYMAN: I think this is in the chest and perhaps just retrosternally, but I do not think this fact is contributory.

DR. WILLIAMS: In the operating room the needle was placed in the third interspace; that is unusual. It was done because the surgeon believed that a later procedure ought to be carried out.

DR. BLAND: What was your opinion when the patient left the operating room?

DR. WILLIAMS: When he left the operating room, the opinion was that he had been greatly relieved by the procedure but that we did not as yet know the diagnosis.

DR. BLAND: It was still not clear whether this was purulent pericarditis or whether the effusion was secondary to other disease.

CLINICAL DIAGNOSES

Pleuropericarditis, pneumococci.
?Pontine hemorrhage.
Coronary-artery disease.

DR. EDWARD F. BLAND'S DIAGNOSES

Pericardial effusion, ?secondary to metastatic disease.
Cardiac tamponade.
Cancer of colon.

ANATOMICAL DIAGNOSES

Subacute suppurative pericarditis, with cardiac tamponade.
Rupture of abscessed and lacerated ascending aorta into pericardium.
Adenocarcinoma of hepatic flexure.
Cerebral atherosclerosis, with recent thrombosis of left anterior and branch of left middle cerebral arteries.
Cerebral infarcts, multiple, old and recent.

PATHOLOGICAL DISCUSSION

DR. ROBERT H. FENNELL, JR.: The heart was covered by shaggy, yellow-gray exudate, which completely encased it and had greatly thickened the epicardium and pericardium. Microscopically, this was a purulent pericarditis that had been present for some time judging from the organization that had occurred. There was a hole, 1 cm. in diameter, in the anterior surface of the aorta, 4 cm. above the ring but within the pericardial sac. The edges were ragged and necrotic. The pericardial cavity was distended at the time of autopsy with 600 cc. of blood, which no doubt came through the hole in the aorta. The sequence of events as I see them is that this patient had pneumonia. Although we found no definite evidence of pneumonia at this time, there were some fibrinous adhesions between the right lung and the pericardium, as well as some adhesions on the other side. Then pericarditis developed as a complication of the pneumonia, and, in the course of the tapping, the adventitia and media of the aorta were lacerated. Free pneumococci in the pericardial cavity localized at the site of the laceration and formed an abscess. Microscopically at this point there was a small abscess involving the adventitia and the media. The terminal event was the rupture of this already partially lacerated and weakened aortic wall. That this patient did not die immediately after the laceration indicated that the laceration had not originally gone through to the lumen. Actual perforation of the aorta by a suppurative pericarditis or pyogenic infection is most unusual. I believe this is the first such autopsy that we have had here in the absence of an endocarditis.

DR. WILLIAMS: What was the explanation for the dyspnea after the last tap? Was there blood through the mediastinum?

DR. FENNELL: No; there was not. It was all within the pericardium. There was some mediastinal emphysema at the time of autopsy. I do not know whether or not that was adequate to explain the dyspnea.

DR. BLAND: What was in the colon?

DR. FENNELL: A well differentiated adenocarcinoma was found at the hepatic flexure of the colon involving a segment 6 cm. long; it had gone through the wall of the bowel but had not metastasized.

DR. BLAND: I do not think we often see such a subacute course with purulent pericarditis. Do you suppose, Dr. Paine, that the initial antibiotic treatment before entry had attenuated the infection a bit and permitted him to carry on?

DR. PAINE: I suspect that that is the answer.

DR. BLAND: Is there anything peculiar about a Type D pneumococcus?

DR. PAINE: No.

DR. EDWARD P. RICHARDSON, JR.: As an incidental finding, there was severe cerebrovascular disease. The large and small arteries contained extensive atheromatosis, and there was recent thrombosis of the left anterior cerebral artery and of a major branch of the left middle cerebral artery. Corresponding to the thrombosis, there was recent cerebral infarction medially in the left frontal lobe, and in the left parieto-occipital region. In addition, there was an old, healed infarct in the left frontal lobe and another, very small, in the right thalamus.

These recent cerebral lesions adequately explain the neurologic changes that occurred terminally. The old lesions, so placed as not to cause any paralysis, major sensory loss or disturbance of consciousness or of intellect, did not produce any apparent clinical symptomatology.

CASE 39032

PRESENTATION OF CASE

A seventy-year-old man was admitted to the hospital because of persistent vomiting.

The patient had a long-standing history of syphilis, adequately treated, and during the last twenty years had had repeated episodes of nausea,

vomiting, belching and burning epigastric pain, lasting days or weeks, previously diagnosed as "gastric crises." Eighteen months before entry, during one of these attacks, a gastrointestinal series was reported as negative. Three and a half months prior to admission he again experienced the onset of "gassiness," abdominal bloating and "heartburn" sensations, transiently relieved by belching and antacids, occasionally relieved by bowel movements and unaffected by ingestion of food. Four weeks before entry he noted marked loss of appetite and desire for cigarettes, and increased abdominal swelling. He felt "terrible." Ten days before entry he began to have vomiting associated with nausea, bloating, restlessness and band-like, "burning and searing" upper epigastric pain. Since that time he had taken almost no food and had vomited most fluid ingested. Three days later he had a brief episode of unsteadiness and dizziness without true syncope. Vomiting persisted, and the patient came to the hospital.

There was no history of jaundice, melena, diarrhea, abdominal cramps or hematemesis. There had been no intolerance to fatty foods but cabbage caused distress. The weight had remained relatively stable. No marked change in bowel habit had been noted.

Physical examination disclosed a well developed, well nourished man who vomited repeatedly. The pupils were round and equal, and reacted to light and on accommodation. The neck veins were flat, and the chest was clear. There was a Grade 2 apical systolic murmur. The aortic second sound was greater than the pulmonic. The abdomen was slightly rounded and more prominent on the right than the left but without a fluid wave. There was slight right epigastric tenderness; peristalsis was quiet. The edge of a mass, interpreted as liver, was palpable 12 cm. below the right costal margin and was tender. The spleen was palpable. No other masses or areas of tenderness were noted. Pressure over the costovertebral angles did not cause pain. The sphincter tone was lax; the prostate was small and slightly tender. There was marked ataxia on walking and marked bony and articular swelling of both knees, with severe bony proliferation and joint effusion without heat or redness. There was intact touch and pain sensation throughout but absent position or vibration sense and tendon jerks in the legs.

The temperature was 99.5°F., the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

The urine had a specific gravity of 1.020 and gave a negative reaction for sugar and a + test for albumin; the sediment contained several clumps of white cells per high-power field. Examination of the blood revealed a hemoglobin of 13.0 gm. per 100 cc. and a white-cell count of 7700, with 76 per cent neutrophils, 20 per cent lymphocytes, 2 per cent monocytes and 2 per cent eosinophils. The nonprotein nitrogen was 34 mg., the bilirubin 0.3 mg. direct and 0.9 mg. total, the alkaline phosphatase 6.2 units, and the amylase 16 units per 100 cc. The prothrombin time was 15 seconds (normal, 13 seconds). A roentgenogram of the chest was normal. A gastrointestinal series showed a normal-appearing esophagus. There was probably a small hiatus hernia of the fundus of the stomach. The stomach was otherwise normal in size and shape and gave no evidence of any organic lesion (Fig. 1). The duodenal cap and proximal small bowel were not unusual. There was a calcified density in a position posterolateral to the stomach, probably in the spleen.

FIGURE 1.

In the hospital the patient had repeated episodes of nausea and vomiting but said that he was hungry. On the second hospital day he had a shaking chill followed by sweating. Questioning disclosed that he had had several such chills during the past few weeks. On gastric aspiration 50 cc. of bile-stained fluid, negative for free acid, was recovered. The cytologic examination of the fluid was reported as negative. A culture of the urine grew out abundant *Bacillus proteus*. During the next four days the temperature ranged between 101 and 102°F., on one occasion rising to 104.5°F., but then dropped to normal after five days of

streptomycin therapy. The fever was not associated with a leukocytosis. Despite the fall in temperature to normal, the patient had persistent retching productive of only small amounts of thin, watery material. He had little, if any, associated abdominal pain although his abdomen was diffusely sore. At this time the examiner thought the mass in the right upper quadrant was cystic and below the lower border of the liver. It was slightly tender, and a hand placed in the right flank could displace it anteriorly. An intravenous pyelogram was normal except for an enlarged bladder.

On the eleventh hospital day an operation was performed.

Differential Diagnosis

Dr. F. Thomas Gephart*: In summary, this seventy-year-old man had an abdominal mass, abdominal pain and a past history of syphilis. I think there is no question that, in spite of treatment for syphilis, he had tabes dorsalis. This is borne out by the ataxia, the reflex changes, the Charcot knee both described on physical examination and noted in the x-ray films, a relaxed anal sphincter and a slightly enlarged bladder. I should like to say that tabes dorsalis is a frequent cause of erroneous diagnosis in surgery. Of 1000 patients with tabes dorsalis seen at Cook County Hospital[1] about 10 per cent had been subjected to needless abdominal operations simply because the symptoms of tabes had mimicked those of an acute abdominal condition.

This patient had a history of eighteen months of severe upper abdominal pain occurring fairly frequently, perhaps I should say increasingly frequently, with nausea and vomiting, which had been diagnosed in the past as gastric crises. From the information given those attacks certainly could have been gastric crises. There are usually three types of this condition: one consists mostly of pain, the second mostly of vomiting, and the third and most common of both pain and vomiting. The pain can be excruciating, and the patient feels extremely ill not only from the vomiting and inability to eat, but from the mental depression that goes with the severe pain and vomiting. I think this is well described by the word "terrible" in the protocol. These attacks tend to occur periodically and may occur with great regularity. However, gastric crises would not explain all the findings. I do want to emphasize also the fact that syphilis, although less common now in the untreated stages, can certainly mimic all the diseases that are associated with the liver, the gall bladder and the upper abdominal organs. Having mentioned that, I am going to discard syphilis as the underlying cause of this man's difficulties.

When reading about the pain and belching unrelieved by antacids, the gassiness and the abdominal bloating, one thinks of hiatus hernia. A small hernia was noted on x-ray examination. However, that would not explain the abdominal mass that was felt, and I shall have to discard that as the sole cause of all this man's symptoms.

Possibly he had pancreatitis. Certainly, these symptoms could go with recurrent bouts of pancreatitis. The one amylase determination was reported as normal. He apparently had no fever with these attacks, which were self-limiting. They certainly could have been recurrent attacks of chronic pancreatitis. That in itself does not explain all the physical findings. The episode of syncope could be explained by the weakness secondary to the vomiting and the lack of ingestion of food. He also had one episode of fever, which, in view of the information given, I am going to attribute to a urinary-tract infection that apparently was subsequently controlled by streptomycin therapy.

Among the findings listed was a round mass in the upper abdomen that was more prominent on the right side. There was apparently no fluid wave in this somewhat distended abdomen. There was some epigastric tenderness, but this was not severe. There was a mass felt that was thought at first to be the liver edge but later appeared to be cystic and somewhat movable. The laboratory findings were not remarkable except for the slightly elevated alkaline phosphatase. The patient apparently had no acute infection on the basis of laboratory findings alone.

May I look at the x-ray films now, Dr. Wyman?

Dr. Stanley M. Wyman: Quite a number of examinations were done. The films of the barium-enema examination show no intrinsic abnormality. The spleen may be slightly larger than usual. The films of the knees are shown simply for the sake of interest to demonstrate the classic changes of Charcot joints. One film selected from the pyelogram shows normal-appearing kidneys. There is evidence of old injection in both buttocks and some calcification in the region of the prostate, all of

*Assistant in surgery, Massachusetts General Hospital.

which are probably unimportant. In the film of the chest the lungs are grossly clear and the heart is somewhat prominent in the region of the left ventricle, but the aorta does not seem abnormal. The most important films are those of the gastrointestinal tract. There is a definite difference between the films of the original examination and those taken almost two years later. On the original films there is no definite abnormality that I can detect. On the second examination I would not agree with the description in the protocol; it seems to me that the lesser curvature of the stomach is indented posteriorly and from the right aspect of the abdomen as though something were pushing on the stomach in this region (Fig. 1). Secondly, there is a thin streak of barium extending upward from the second portion of the duodenum; it is poorly seen on this second film, but I think it is present and it seems to lie in the expected location of the common duct. Calcification in the spleen is as recorded in the protocol.

DR. GEPHART: Is there any deformity of pressure on the duodenum?

DR. WYMAN: It is quite possible that there is slightly more pressure than usual on the second and third portions, but it is not striking. The main pressure on the upper gastrointestinal tract seems to be along the lesser curvature of the stomach. I do not see any evidence of invasion or involvement of the mucosa, and I do not see any intrinsic abnormality in the stomach itself.

DR. WALTER ST. GOAR: I should like to add that this patient had a bromsulfalein retention of 28 per cent. Also, the right-upper-quadrant mass that was difficult to define on physical examination was not diffusely tender. When asked to do so, the patient consistently pointed with one finger to a tender area the size of a silver dollar just below the right costal margin in the midclavicular line.

DR. GEPHART: There was evidence on both physical and x-ray examination of a mass in the upper abdomen. One can raise a number of possibilities to explain this. The first is a cyst of the kidney, but I think on the basis of a normal pyelogram that can be eliminated. Secondly, in a patient with a history of syphilis, one thinks of an aortic aneurysm. I suppose, in the absence of pulsation, we can eliminate aneurysm as the cause of these difficulties. A cyst of the liver, spleen, omentum or retroperitoneal tissue is also a possibility. Here the spleen is fairly well outlined so that can be eliminated.

My diagnosis of the cause for this x-ray shadow, the patient's pain and also this mass on examination is a pancreatic cyst. I also think it is possible that he had infection of the gall bladder and some associated pericholecystitis. However, there are a number of things that I think point toward pancreatic cyst. Although he gave no definite history of trauma — only 15 to 30 per cent of patients give such a history — he did give a history that is consistent with pancreatitis. Sometimes this is thought to be an antecedent cause although Judd[2] has reported from the Mayo Clinic that pancreatitis was found in only 4 out of 47 cases of pancreatic cyst. The duration of the illness is about average for pancreatic cyst. Such cysts have been known to be present for at least twenty years, but usually about a year more or less is the course of the disease before the patient comes to medical attention. The early manifestations of pancreatic cyst are usually vague; there may be slight anorexia gradually increasing to complete anorexia. Upper epigastric discomfort is gradually replaced by actual pain. Frequently there is nausea and vomiting as in this case and, therefore, associated weight loss. Sometimes constipation occurs from pressure of the cyst on the colon. Often there is, for some reason or other, a definite cyclic schedule for the recurrence of these bouts of pain, and the course is usually progressive. Of all the signs and symptoms pain is usually the most pronounced although it is not a distinctive symptom of this condition; it is reported as being present in 85 to 90 per cent of the cases at the Mayo Clinic. As already mentioned, loss of weight and sometimes jaundice are present. About 30 per cent of the patients with pancreatic cyst have been reported to have associated gallbladder disease. An important point in diagnosis is the x-ray findings. I think that the deformity in the stomach could be best explained by cyst, but from the x-ray films alone one could not tell whether it was a mesenteric cyst or some other form of retroperitoneal cyst.

A liver cyst could conceivably cause this picture. I doubt if it would cause quite as much pain and the other symptoms that this patient had. One condition that I should bear in mind as a possibility is a chronic cholecystitis with perhaps an acute flare-up in the past, perforation of the gall bladder and abscess formation around the gall bladder.

Perhaps those severe episodes of pain in the past were bouts of acute cholecystitis and were passed off as being tabetic crises. Three or four years ago we had a patient who was a morphine addict, with cholecystitis, whose bouts of pain had been masked by the morphine. He had a similar upper abdominal mass, which at operation was found to be an acute and chronically infected gall bladder as well as a pericholecystic infection.

I should like to make a diagnosis of tabes dorsalis and pancreatic cyst.

Dr. R. S. Shaw: When we saw this patient our diagnosis lay between an acute cholecystitis and a pancreatic cyst. As was noted by Dr. St. Goar, the right-upper-quadrant mass was not clearly defined, and the medial margin could not be made out. We thought the patient probably had a pancreatic cyst because of the deformity of the stomach in the x-ray film and because this case did not follow the usual pattern of subsiding acute cholecystitis. Clinically, he grew much worse as the leukocytosis and fever decreased. We scheduled him for operation with a diagnosis of pancreatic cyst.

Clinical Diagnoses

Pancreatic cyst.
Tabes dorsalis.

Dr. F. Thomas Gephart's Diagnoses

Pancreatic cyst.
Tabes dorsalis.

Anatomical Diagnoses

Acute and chronic cholecystitis.
Cholelithiasis.
(Tabes dorsalis.)

Pathological Discussion

Dr. Shaw: Under anesthesia the mass was easily palpable in the right upper quadrant and was unmistakably gall bladder. When the abdomen was opened a large, acutely inflamed gall bladder was found with a small amount of purulent exudate about it and many old and new adhesions to omentum and transverse colon. The gall bladder contained milk bile, and a 1.5-cm. stone was impacted in the ampulla. We could find no abnormality whatever in the pancreas or stomach and could not explain the deformity of the stomach that is seen in the x-ray film. The spleen was of normal size, and there was no other disease in the abdomen. Cholecystectomy was performed. The cystic duct was small; the common duct appeared normal and was not explored.

Postoperatively, severe nausea continued for about two weeks, with much retching and hiccuping, but thereafter the patient rapidly improved and stated that he felt better and ate better than he had in five years.

Dr. Robert H. Fennell: Microscopically, the gall bladder showed not only acute inflammation but also quite a bit of old inflammatory process; it was thickened and scarred. There were several abscesses in the wall that completely destroyed it and at one point extended through to the omental fat. From the histology one would suppose that it had been going on for months, perhaps years. Going back over the patient's record, I tried to demarcate a line where the tabes ended as the cause of the symptoms and where the cholecystitis began. We also questioned the patient and could not delineate any clear line.

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SEVEN AGES OF FOUNDATIONS

The John and Mary R. Markle Foundation, having reached the ripe age of twenty-five, has taken stock of its own growing pains in its annual report for 1951. From the vantage point of mature years and an endowment of about $17,000,000 and after successive excursions into the fields of social welfare, medical research and medical education, the Foundation is ready to undergo analysis and pass on some words of advice to youngsters with only a few years' experience in the business of philanthropy:

> It is not easy for foundations to reach maturity. All must go through the stages of learning to walk, meeting the hazards of early childhood and suffering the pangs of growing up. Many, as they grow, develop the necessary self-confidence and judgment to make a real place for themselves in the philanthropic world. In the nature of things a free foundation starts life because of a donor who has a tremendous desire to do something worth while for mankind [and some material resources to accomplish his deeds, it may be added parenthetically].

The report stresses the responsibility of all foundations to devise means through which to give money, a responsibility that presents difficulties particularly to the brash young newcomers — the "foundations with no endowment, collecting money on an emotional basis from the public, foundations supported by industries interested in the health of their employees and the longevity of human beings, and foundations supported by government for the protection of the nation."

The latest device through which to give money, adopted not by a newcomer but by the mature John and Mary R. Markle Foundation, was the result of a policy established in 1948. Since that year 90 scholars have been appointed for a five-year full-term tenure, 86 of whom still remain in 49 medical schools. The experiment is too new to be evaluated fully, but there is little question that it represents a justified pioneer venture. The objective is to step in and come to the aid of promising young scientists when, several years after postgraduate degrees have been received, they have demonstrated their promise but find heavy and insistent economic demands upon them to earn a living. The Markle Foundation stands ready to come to the support of many of these men for five crucial years when their whole careers are at stake, and at a period of life when society as well as the individual is trying to weigh promises for the future against the operational demands of the present.

The final value of the promissory notes will be no more accurately determined than the final value of the Markle grant-in-aid program conducted during its adolescence in the late thirties and early forties. The bound volumes of publications acknowledging indebtedness to the Foundation are observed in the report to require more space than the Five-Foot-Shelf or the Great Books although no claim is made regarding which of the three constitutes the most valuable library.

In any event the first twenty-five years of the Markle Foundation have unquestionably been

productive, and the present direction of its program is bold and new and being followed by educators and investigators with much interest.

At twenty-five years of age one has, indeed, a full claim to the status of maturity. On the other hand, the seven ages of man have not been accomplished, there is work to be done, and the future can be counted upon to bring changes, some mistakes, some progress and even greater wisdom. The twenty-fifth birthday is a landmark at which mature institutions as well as persons enjoy the prospect of the next quarter of a century with the necessary self-confidence and judgment to make a real place for themselves in a world that is not always philanthropic.

STUDIES OF REGIONAL MEDICAL CARE

The Hospital Council of Greater New York was organized in 1938 primarily to "advise the public of New York City and the co-operative fund-raising agencies concerning the financial needs of hospitals and related facilities, both for capital and operating purposes." As a joint effort of about 20 leading voluntary and governmental health, hospital, medical, welfare and business organizations of the State, it set about its task by a thorough fact-finding study of hospital services in the metropolitan area. The survey, under the leadership of the late Dr. John B. Pastore, collected data basic to community hospital planning such as the relation between hospital facilities and local population densities in various parts of the City, and this was further broken down into special services such as obstetrics and tuberculosis and correlated with existing and anticipated birth rates and disease trends. The Council, which has a close working relation with the United Hospital Fund of New York City, was soon in a position to give informed advice concerning whether in a given area of the City certain hospital services needed to be expanded or, perhaps, converted to other purposes. In the course of time, the recommendations of the Hospital Council have come to carry great weight both in rallying support for institutions in need of expansion and in avoiding duplication of facilities. Indeed, in recent years all Hill–Burton allocations within Greater New York have been made in accordance with recommendations of the Council. Obviously, the Hospital Council of Greater New York has made a major contribution to the effective and economical utilization of the health services in its community.

It is gratifying, therefore, to learn that a committee of the United Community Services of Boston is undertaking a project along similar but somewhat broader lines. The initial or planning phase of the program has been made possible by a grant from the Rockefeller Foundation for $10,000 and from the Permanent Charities Fund for $2,000. When the plan of action has been completed, the program will move into three successive phases: the establishment of base lines; the setting up of demonstrations of regional co-ordination in an urban area; and the evaluation of the improvements that have resulted from the program.

In setting up desired base lines, the Committee proposes to study the distribution and availability of inpatient and outpatient hospital facilities according to types of accommodations and adequacy by accepted standards, the effect of specialization in and by hospitals on the utilization of facilities, the availability of hospital privileges to the medical profession and the degree and manner in which these privileges are utilized, the distribution and utilization of expensive medical equipment and personnel, the use of general-hospital beds for long-term cases of chronic disease and the use of hospital beds by patients undergoing diagnostic study.

When this phase of the program is completed, Metropolitan Boston will have an itemized inventory of its health services with, for the first time, some indication of the adequacy of each service in relation to the strictly local as well as the broad community needs. This should serve a twofold purpose in demonstrating deficiencies and in furnishing a basis for evaluating subsequent improvement in services. It is a common-sense approach to a complex problem.

WHO READS MAY RUN

Every periodical with other than an almost completely frozen circulation, as might be the case with one that served only the members of a society with a very slow turnover, has a constantly shifting subscription list. This revolving popularity, since a

certain number of discontinuing subscribers may return again at a later date to seek additional intellectual succor, might be likened to a sort of *folie circulaire*; even more fanciful, but with a touch of realism, would be the comparison with a tapeworm that adds new segments at one end, even as he (or she) sheds older, fully ripened ones at the other.

Whatever simile is used, if any, the fact remains that a journal with an independent subscription list of any size loses annually many subscribers and must add many new ones to make up the loss. Obviously, the continued growth of the circulation must depend on taking on more than are lost, and it is equally obvious that conservation of old subscribers should be a more economical process than gaining new ones. Old subscribers, however, have tasted the bait and have at least some familiarity with the periodical that they are abandoning. Through them, therefore, information can be gained in regard to the value of that which they are giving up, with regret or relief. It is apparent that if old readers are dissatisfied, new ones are likely to become so in turn.

It has long been the custom with this journal, when a subscriber has failed to renew after a reasonable time has elapsed and a gentle reminder or two have been issued, to send a final message asking the reason for the default. A surprising number of replies are received in response to this questionnaire, which is sent out in a spirit of pure scientific research mingled with humility and with no intention of high pressuring the individual into a subscription renewal.

An analysis of 300 such replies selected at random from those received in 1952 demonstrated a total volume of 312 good reasons, divided into 7 groups, for letting the subscription lapse. A dozen persons had therefore two good reasons, a fact that would be taken seriously by any statistician. In order of frequency expense led with 110 erstwhile subscribers, followed by 54 who had failed to renew through oversight and constituted a class that was largely redeemable; 44 had insufficient time for reading the *Journal*; 41 used library copies; 23 were in service; 21 read specialty journals only, and 19 were, for one reason or another, dissatisfied.

It must be apparent to the most unsophisticated reader that had 19 of these 300 former subscribers let their subscriptions lapse because of expense and 110 because of dissatisfaction, the figures would not have been made public, and the editors would be requadrupling instead of merely redoubling their efforts to improve the quality of the publication.

PROFESSOR OF SURGERY

In New England among the oldest medical institutions are to be found the most vigorous. This may rightly give one heart, but also boding well for the future of medicine in this region is the observation that new institutions, like the recently organized Department of Surgery at Tufts College Medical School, the Pratt Diagnostic Clinic and the New England Center Hospital, take root and flourish in their contribution to medical care and knowledge. For medicine, like love, is not Time's fool, nor can it appropriately be described as "old and gray and full of sleep and nodding by the fire."

Dr. Charles G. Child, III, formerly associate professor of clinical surgery, Cornell University Medical College, has been named to succeed Dr. C. Stuart Welch, the first full-time Tufts professor of surgery, and as Dr. Welch returns to Albany it is fitting to note that his mark here will endure. Those who know him best most regret the personal tragedy that impelled him to the decision to return to private practice.

Dr. Child is immediately notable among Boston's professors of surgery in being the only one wholly trained in surgery outside New England. He is well prepared to assume the responsibility of a department already organized on the triangular base of teaching, research and surgical practice. He is an advocate of a general surgery not restricted to the abdomen, properly regarding the ribs as a most admirable retracting device rather than a forbidding cage. His bibliography suggests that he will have much for which to account, unlike Johnson's Physicker Levet, of whom it was surmised, "sure the Eternal Master found the single talent well-employ'd." Ranging over the subjects of experimental hypertension, shock, fluid and electrolyte balance, surgery of cardiospasm and of cancer of the duodenum and of the pancreas and the

hepatic circulation, as well as gangrene and guanidine, it speaks for his broad scope.

Tufts and the other units of the New England Medical Center deserve commendation in the selection of Dr. Child as successor to Dr. Welch, who set high standards in the execution of his manifold tasks. The signs augur well for the future.

A physician in Chicago has turned drayman, says a paper of that city. Doctors were too numerous for him to succeed in his profession, but by a change of business, he is now thriving.

Boston M. & S. J. *January 19, 1853*

MASSACHUSETTS MEDICAL SOCIETY

STATED MEETING OF THE COUNCIL

A stated meeting of the Council will be held in John Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Wednesday, February 4, at 10:30 a.m. This meeting will be followed by the Cotting Luncheon.

Business:

1. Call to order at 10:30 a.m.
2. Presentation of record of meeting held October 1, 1952, as published in Supplement No. 2, November 27, 1952.
3. Reports of standing and special committees.
4. Such other business as may legally come before this meeting.

ROBERT W. BUCK, M.D.
Secretary pro tempore

OFFICIAL DIRECTORY

The official directory of officers and fellows of the Massachusetts Medical Society, as of August 1, 1952, with supplementary names, has been distributed to the councilors of the Society and is available to all fellows on request.

Every effort has been made to avoid errors, but it is probable that some will be discovered. Fellows are urged to check their own and other listings and to report promptly any mistakes they may discover in names, addresses, specialty listings or other matters to the Secretary, Massachusetts Medical Society, 22 Fenway, Boston 15, Massachusetts.

DEATHS

HAGERTY — Joseph J. Hagerty, M.D., of Norwood, died on December 10. He was in his seventy-ninth year.

Dr. Hagerty received his degree from Harvard Medical School in 1905. He was one of the incorporators and a former member of the board of trustees of the Norwood Hospital and was a member of the New England Roentgen Ray Society and Radiological Society of North America.

He is survived by a brother and three sisters.

STONE — Moses J. Stone, M.D., of West Roxbury, died on December 14. He was in his fifty-eighth year.

Dr. Stone received his degree from Tufts College Medical School in 1921. He was assistant professor of medicine at Boston University School of Medicine, chief of staff of the Jewish Tuberculosis Sanatorium in Rutland, Vermont, chief of the outpatient chest clinic, Beth Israel Hospital, and a member of the staff of Massachusetts Memorial Hospitals, and was a member of the American Trudeau Society, American College of Chest Physicians and New England Roentgen Ray Society and a fellow of the American Medical Association.

He is survived by his widow, three children, four brothers and two sisters.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

STANDARDS FOR DAY CARE OF CHILDREN

A bulletin entitled "Recommended Minimum and Preferred Standards for Agencies Giving Day Care to Children Under Seven Years of Age" has recently been prepared and published by the Department of Public Health. This publication is the result of combined effort to implement recommendations of the Massachusetts Committee of the Midcentury White House Conference on Children and Youth and to assist Massachusetts Boards of Health in carrying out the licensing requirements of such agencies.

In 1951 a committee on day-care recommendations of the White House Conference was established under the auspices of the United Community Services of Metropolitan Boston, 14 Somerset Street. This committee consists of representatives of the Child Care Council of that organization, the former Subcommittee on Child Day Care, the Associated Day Care Services of Metropolitan Boston and the departments of Education, Mental Health, Public Health and Public Welfare of the Commonwealth of Massachusetts.

CORRESPONDENCE

IN LIEU OF SOCIAL SECURITY

To the Editor: Social Security programs do not include the physician, the lawyer, the architect, the accountant, the engineer, the clergy, the dentist, the funeral director and other professional groups not in regular employment. This is not an oversight, but is a decision of our law makers based on the sound premise that these professional persons have incomes sufficient to make their own financial arrangements, investments and income-producing plans to assure adequate retirement when their ability to earn has diminished or terminated. Some professional people have made insurance provisions, some have acquired income-producing stocks or

bonds, and many have made imprudent investments, to their great grief. The greatest number, however, have decided to make profitable investments but do not have enough immediate cash ahead to take the contemplated step. Consequently, as months and years roll by, things remain where they were — undone.

Here is a ready answer to many who have this problem to contend with. The Government has provided a Series E Defense Bond in seven denominations, — from $25 to $10,000, — all of which can be purchased for 75 per cent of their redemption value, maturing in nine years and eight months and paying 3 per cent interest to maturity. One may extend these bonds for an additional ten years by merely holding them after maturity, thereby returning an additional 33⅓ per cent over the face value for the extended time. In the event that an emergency arises, they can be cashed at any time after they are sixty days old.

All commercial banks where a professional man may carry a checking account have made the "bond-a-month" plan available to depositors. Under this plan a depositor executes a simple order to the bank, which he authorizes to issue a bond of a selected denomination every month, charging the issue price of the bond to his checking account and deducting it from his monthly balance. The bond is delivered regularly each month to the depositor. This order may be increased, decreased or terminated at will. The procedure is automatic, and the bonds begin to accumulate.

Twenty years from the time this process begins, the bonds become available for current income, paying the face value as well as a third earned during the extension period, thus providing a nice income with regularity from an investment in the safest security ever known. This has an advantage over insurance or social-security plans in that if a part of the accumulation is needed to meet unforeseen expenses or an emergency, all that has to be done is to take enough of the bonds to the nearest bank for immediate payment, the redemption value at any given time being computed from the issue date appearing on the face of the bond.

The procedure is as simple as that, and the story is complete. Physicians should look into it the next time they make a bank deposit.

ALFRED C. SHEEHY
Deputy State Director
Savings Bonds Division
United States Treasury Department

Boston

MISCELLANY

CAMPAIGN AGAINST MUSCULAR DYSTROPHY

More than 100,000 persons in this country are now sufferers from muscular dystrophy, of whom over 65,000 are in the younger age groups, according to an estimate of the Muscular Dystrophy Associations of America, Incorporated.

This organization is currently conducting a campaign for funds for research into the nature of this disease and its treatment, having already established 17 research projects during the past year.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Principles and Practice of Aviation Medicine. By Harry C. Armstrong, M.D., The Surgeon General, United States Air Force. Third edition. 8°, cloth, 476 pp., with 97 illustrations. Baltimore: Williams and Wilkins Company, 1952. $7.50.

The first edition of this book was published in 1939, and reprinted four times before the issuance of the second edition in 1943. This new edition has been thoroughly revised and brought up to date. The publishing is excellent, and the book is recommended as a standard handbook on the subject.

Textbook of Clinical Parasitology. By David L. Belding, M.D. Second edition. 8°, cloth, 1139 pp., with 283 illustrations. New York: Appleton-Century-Crofts, 1952. $12.00.

The text of this second edition of a standard work has been revised and brought up to date. The first edition was published in 1942, and during the intervening decade there has been extensive progress in the field of parasitology. New material has been added on amebiasis, trypanosomiasis, leishmaniasis, malaria and schistosomiasis. New procedures have been included in the section on diagnostic methods, and chemotherapeutic agents have been added to the list of drugs. A new chapter has been written on insecticides and repellents. Lists of references are appended to the appropriate chapters. There is a comprehensive index, and the book is well published. It is recommended for all medical libraries and private collections on the subject.

Management of the Newborn. By Arthur H. Parmelee, M.D., professor of pediatrics, University of Southern California School of Medicine, and senior attending pediatrician, Los Angeles Children's Hospital. 8°, cloth, 358 pp., with 47 illustrations. Chicago: Year Book Publishers, Incorporated, 1952. $7.00. (*General Practice Manuals.*)

The author has written a manual on the newborn from both the normal and clinical points of view. The material is well arranged. The first part of the text deals with the fetus, birth and neonatal adjustments, characteristics, care and management, with a chapter on the premature infant. The final chapters discuss the disturbances and diseases due to birth processes, abnormal variations of physiologic peculiarities, prenatal factors and acquired infections and other postnatal factors. The text is well written. Lists of selected references are appended to the various chapters, and there is a good index. The publishing is excellent. The author has not endeavored to write a textbook but has produced a valuable manual on his subject.

Psychotherapy with Schizophrenics. Edited by Eugene B. Brody and Frederick C. Redlich. With an introduction by Robert P. Knight. 8°, cloth, 246 pp. New York: International Universities Press, 1952. $4.00. (Monograph Series on Schizophrenia No. 3.)

This volume is made up of seven papers read at various meetings during 1950 and 1951, with their discussions. The publishing is good, and the book should be in collections on mental disorders and psychotherapy.

Medical Certification of Cause of Death: Instructions for physicians on use of international form of medical certificate of cause of death. 8°, paper, 20 pp. Geneva, Switzerland: World Health Organization, 1952. 20c. Available also in a French edition. (*Bulletin of the World Health Organization*, Supplement 3.)

This pamphlet contains a copy of the international form of medical certificate of cause of death at the *Sixth Decennial International Revision Conference*, held in Paris in 1948. The cause of death is defined as the underlying cause: the disease or injury that initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence that produced the fatal injury. Most of the text is devoted to a discussion of a proper death certificate. An annex lists examples of incomplete descriptions of cause of death.

Endoscopy: As related to diseases of the bronchus, esophagus, stomach, and peritoneal cavity. By Edward B. Benedict, M.D., assistant clinical professor of surgery, Harvard Medical School, and endoscopist, Massachusetts General Hospital. 8°, cloth, 373 pp., with 130 illustrations and 12 plates. Baltimore: Williams and Wilkins Company, 1951. $10.00.

This new book covers the whole field of endoscopy, including bronchoscopy, esophagoscopy, gastroscopy and peritoneoscopy, separate parts being devoted to each of these divisions. Lists of selected references are appended to the various chapters in the different parts, and there are separate indexes of authors and subjects. The book not only surveys the important literature but also embodies the extensive experience of the author. The illustrations, in color and black and white, and the publishing are excellent. The book is recommended for all medical libraries.

Current Therapy 1952: Latest approved methods of treatment for the practising physician. Editor, Howard F. Conn, M.D. 4°, cloth, 849 pp. Philadelphia: W. B. Saunders Company, 1952. $11.50.

Many physicians contributed new methods to this latest volume in an important series summarizing treatment in all the fields of clinical medicine and the specialties. The printing is good, with a good type, and there is an extensive index. The book should be in all medical libraries and should prove valuable as a reference tool.

Etiology and Diagnosis in the Treatment of Infertility in Men. By Robert S. Hotchkiss, M.D., professor and chairman, Department of Urology, New York University-Post Graduate Medical School, visiting surgeon-in-charge (urology), Bellevue Hospital, and visiting surgeon-in-charge (urology), University Hospital. 8°, cloth, 73 pp., with 15 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $2.50. (Publication No. 53, *American Lecture Series.*)

This small monograph has been written for physicians who may have to deal with barren couples. The subject is adequately covered in its various aspects, and there is a bibliography and an index.

Fractures and Joint Injuries. By Sir Reginald Watson-Jones, B.Sc., M.Ch.Orth., F.R.C.S., Orthopaedic Surgeon to His Majesty the King, director, Orthopaedic and Accident Service, The London Hospital, senior surgeon to the Robert Jones and Agnes Hunt Orthopaedic Hospital, and civilian consultant in orthopedic surgery to the Royal Air Force. Vol. I. Fourth edition. 8°, cloth, 443 pp., with 709 illustrations. Baltimore: Williams and Wilkins Company, 1952. Price per set of two volumes $22.00.

This standard work was first published in 1940 and, in addition to three previous editions, was reprinted three times. This new edition has been thoroughly revised and new material added in Vol. I on wound shock and the adaptation syndrome in its relation to shock, the treatment of open fractures and joint wounds, chemotherapeutic control of infection, early closure of wounds by secondary suture or skin grafting, and plastic surgery in fracture treatment, transplantation of bone, cancellous bone grafting, intermedullary nailing and fatigue and pathologic fractures. A series of cases, illustrating typical bone-grafting operations, has been included. Vol. I is divided into two parts: principles of fracture treatment; and fatigue or stress, birth and pathological fractures. Two color portraits of Hugh Owen (1834–1891) and Robert Jones (1857–1933), precede the text. References are carried as footnotes on the pertinent pages. The illustrations are excellent, many being in color. There are indexes of authors and subjects, and the book is well published. The printing was done in Great Britain. The set should be in all collections on the subject.

Formulary of the Massachusetts General Hospital and the Massachusetts Eye and Ear Infirmary. 1951. Prepared by the Pharmacy Committee; by authority of General Executive Committee. Edited by John T. Murphy, pharmacist-in-chief. 16°, cloth, 155 pp. Boston: Massachusetts General Hospital, 1951. $1.25.

This formulary lists the preparations authorized for use in both hospitals. The material is divided into three main classes: enteral, parenteral and topical use. There is an extensive index of twenty-nine pages, arranged by the names of the preparations.

The Thoracic Surgical Patient: Preoperative, anesthetic and postoperative care. By Lew A. Hochberg, M.D. With a foreword by Frank B. Berry, M.D. 8°, cloth, 364 pp. New York: Grune and Stratton, 1952. $8.75.

This book, which is the joint work of seven specialists, is based on the experience gained in the care of thoracic cases at the Kings County Hospital. Believing that a "chest condition" is better cared for postoperatively by the correction of preoperative abnormalities whenever possible before surgery is instituted, the author has written an extensive chapter on basic physiology and pathologic physiology. He is also responsible for the chapters on anesthesia and rehabilitation. The various chapters discuss the injuries, anomalies and diseases of the chest wall, empyema, collapse therapy, pulmonary resection, the esophagus, mediastinum, diaphragmatic hernia and cardiovascular surgery. In addition to the various types of care, short descriptions of diseases and complications are presented under the various headings. There is an extensive bibliography and a good index, and the book is well published. It should be in all collections on chest surgery.

Hippocrates on Intercourse and Pregnancy: An English translation of On Semen and On the Development of the Child. By Tage U. H. Ellinger, Sc.D., M.A. With an introduction by Alan F. Guttmacher, M.D. 16°, cloth, 128 pp. New York: Henry Schuman, 1952. $2.50.

For the first time this important text of the Hippocratic codex has been translated into English. It had appeared earlier in French in Littré's monumental edition of Hippocrates, *Oeuvres complètes d'Hippocrate* (Paris, 1851).

Fluid Balance: A Clinical Manual. By Carl A. Moyer, M.D., professor of surgery, Washington University School of Medicine. 12°, cloth, 191 pp., with 20 tables and frontispiece. Chicago: Year Book Publishers, Incorporated, 1952. $3.75.

The author discusses the body fluids in general, and the fluid and electrolyte imbalances, their diagnosis and treatment. There is a chapter on the complications of parenteral fluid therapy. Short lists of references are appended to the chapters and there is an excellent index.

The Doctors Jacobi. By Rhoda Truax. 8°, cloth, 270 pp. Boston: Little, Brown and Company, 1952. $3.50.

This book constitutes the life stories of Mary Putnam Jacobi and her husband, Abraham Jacobi, both noted American physicians. The composite biography is written in a pleasing, conversational style and should be in all medical history collections.

Doctors in Blue: The medical history of the Union Army in the Civil War. By George W. Adams. 8°, cloth, 253 pp. New York: Henry Schuman, 1952. $4.00.

This history is based on an extensive study of all available records and information and portrays the state of military medicine and surgery during the period of the Civil War. A list of source material and an index conclude the text. The book should be in all historical collections.

Topics in Physical Chemistry: A supplementary text for students of medicine. By W. Mansfield Clark, Ph.D., Sc.D., DeLamar Professor of Physiological Chemistry, Johns Hopkins University School of Medicine. Second edition. 8°, cloth, 777 pp., with illustrations and tables. Baltimore: Williams and Wilkins Company, 1952. $10.00.

This new edition of a book first published in 1948 has been revised and in some places rewritten. It is designed to serve as a reference work for the medical student and for persons interested in elementary biochemistry. The whole field of the subject is covered, and the book should prove valuable for reference. There is an extensive index, as well as a table of logarithms and proportional numbers. The publishing is excellent. The printing is done with a good type of soft, light, nonglare paper.

Refraction Correlated with Optics and Physiological Optics and Motility Limited to Heterophoria. By Walter B. Lancaster, M.D., D.Sc.Hon. 8°, cloth, 310 pp., with 99 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $7.75.

The late Dr. Lancaster wrote this book to supplement the material usually found in works on refraction and motility. The author served for thirty-five years on the American Board of Ophthalmology, and it was his considered opinion that the present work was needed for the purpose of educating the average ophthalmologist to the importance of having a knowledge of the principles of optics and physiologic optics. The text proper is divided into approximately equal parts on optics and physiologic optics, and on the errors of refraction and motility. Two appendixes are devoted to questions, problems and answers on refraction and motility, and notes on formulas and magnification. The book should be in all collections on ophthalmology.

Office Endocrinology. By Robert B. Greenblatt, M.D., C.M., professor of endocrinology, Medical College of Georgia, chief of endocrinology, University Hospital, director of Endocrine Clinic, University Hospital, consultant to the Surgeon General, United States Army, consultant to Lenwood Hospital, United States Veterans Facility, and special consultant, United States Public Health Service. With a foreword by G. Lombard Kelly, M.D., president, Medical College of Georgia. Fourth edition. 8°, cloth, 561 pp., with illustrations and plates. Springfield, Illinois: Charles C Thomas, 1952. $10.50.

The first edition of this standard book was published in 1941. The text has been rewritten to a large extent, including the addition of twenty chapters. The book, which is written for the general practitioner, is based on the personal experience of the author in office, clinic and laboratory. Lists of selected references are appended to the various chapters. There are indexes of authors and subjects. The publishing is excellent.

Oral Medicine: Diagnosis and treatment. By Lester W. Burket, D.D.S., M.D., Sc.D., professor of oral medicine and dean, School of Dentistry, University of Pennsylvania, professor of oral medicine, University of Pennsylvania School of Medicine, chief, Oral Medicine Service, Philadelphia General Hospital, and consultant to the Army, Navy and Veterans Administration. With a chapter on oral cancer by S. Gordon Castigliano, M.D., chief, Department of Head and Neck Tumors, American Oncologic Hospital, Philadelphia, professor of oncology, Temple University School of Dentistry, Philadelphia, and associate in oncology, University of Pennsylvania School of Medicine. Second edition. 4°, cloth, 575 pp., with 372 illustrations. Philadelphia: J. B. Lippincott Company, 1952. $14.00.

This second edition of a book first published in 1947 has been thoroughly revised and brought up to date. A chapter on oral cancer, written by Dr. S. G. Castigliano, has been added. Many chapters have been rewritten, and the bibliographies and illustrations revised. The text is printed in a two-column format, and there is an extensive index. The book should be in all medical libraries.

Developmental Disorders of Mentation and Cerebral Palsies. By Clemens E. Benda, M.D., director of research and clinical psychiatry, Walter E. Fernald State School, Waverley, Massachusetts, instructor in neuropathology, Harvard Medical School, assistant in psychiatry, Massachusetts General Hospital, and lecturer, Postgraduate Seminar, Massachusetts Department of Mental Health. 8°, cloth, 565 pp., with 102 illustrations. New York: Grune and Stratton, 1952. $12.75.

This new book on an important subject is based on the author's experience of over fifteen years in various research institutions. The pertinent literature has been surveyed and evaluated. The material is divided into five parts as follows: antenatal developmental disorders; cerebral palsies; metabolic disorders and degenerative diseases; total personality disorders; and principles of treatment. An appendix graphically portrays the sterilization laws in the United States. Bibliographies are appended to the chapters, and there are indexes of authors and subjects. The book is well published and should be in all collections on the subject.

Biochemistry for Medical Students. By William V. Thorpe, M.A., (Cantab.), Ph.D. (Lond.), reader in chemical physiology, University of Birmingham. Fifth edition. 8°, cloth, 528 pp., with 41 illustrations. Philadelphia: J. B. Lippincott Company, 1952. $6.00.

The first edition of this British book was published in 1938, and five editions and four reprintings speak well for its soundness and popularity. This new edition has been thoroughly revised and brought up to date. Much of the text has been rewritten, and material added. The chapters on metabolism have been largely rewritten to include the tricarboxylic acid cycle of Krebs in its proper perspective. There is a good index. The printing was done in Great Britain.

The Fight Against Tuberculosis: An autobiography. By Francis M. Pottenger, M.D. 8°, cloth, 276 pp., with 3 illustrations and frontispiece. New York: Henry Schuman, 1952. $4.00.

In this biography Dr. Pottenger tells the story of his life from boyhood to the present time, when he has reached the age of eighty years. He is internationally known for his work in the prevention and control of tuberculosis, and he treats this phase of his life very fully. He originally wrote this history of his life for his children and presented it to them at Christmas in 1934. Appended to the text is a bibliography of the publications of the author. The book should be in all collections on medical history.

Medical Disorders of the Locomotor System, Including the Rheumatic Diseases. By Ernest Fletcher, M.A., M.D. (Cantab.), M.R.C.P., physician-in-charge of the Department of Rheumatism and lecturer on rheumatic diseases, Royal Free Hospital, approved University teacher, University of London, physician to the Arthur Stanley Institute, Middlesex Hospital, consulting physician to Queen Mary's Hospital for the East End, Heberden medallist and lecturer in rheumatism, and member of the Scientific Advisory Committee, Empire Rheumatism Council. Second edition. 8°, cloth, 884 pp., with 377 illustrations. Baltimore: Williams and Wilkins Company, 1951. $11.00.

Dr. Fletcher has thoroughly revised the second edition of his book, first published in 1947. New chapters and sections include discussions of pain, the physiology and pathology of bone, synovial fluid, laboratory findings, neuralgia and neuritis, the collagen diseases, psychiatric aspects, hydrotherapy and the antibiotics. Fourteen specialists have contributed chapters to the work. An appendix discusses cortisone and ACTH. There are indexes of authors and subjects, and the publishing is excellent. The printing was done in Great Britain.

Transactions of the American Goiter Association, 1951 Annual Session, May 24, 25, and 26, Deshler-Wallick Hotel, Columbus, Ohio. 4°, cloth, 506 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1951. $12.50.

This volume of transactions for the year 1951 features symposiums on iodine metabolism, the diagnosis and medical treatment of toxic goiter, thyroiditis, surgical aspects of goiter and thyroid tumors. Included are the Van Meter prize-award essay by Dr. I. N. Isenberg, of Boston, on column chromatography of thyroid-gland hydrolysates, and the presidential address of Dr. T. C. Davison on chronic hyperthyroidism. These transactions contain fundamental material, and complete sets should be in all regional medical libraries.

Differentialdiagnose innerer Krankheiten: Eine kurzgefasste Darstellung für Ärzte und Studierende. By Dr. Robert Hegglin, Privatdozent, University of Zürich. 8°, cloth, 454 pp., with 220 illustrations. Stuttgart: Georg Thieme, 1952. Ganzleinen DM 49.80. (Distributed by Grune and Stratton, New York.)

Dr. Hegglin has written a typical, comprehensive book on the differential diagnosis of internal diseases. The material is arranged in a systematic order, beginning with general symptomatology, followed by diseases of the blood and blood-forming organs, respiratory, circulatory and renal disorders, hypotonia, edema, fever, pain, diarrhea, icterus and disturbances of consciousness. The relevant literature is surveyed, and there is a comprehensive index of thirty-one pages. The book should prove valuable to German-reading physicians.

NOTICES

ANNOUNCEMENT

Dr. J. Joseph Klar announces the removal of his office from 38 Maple Street, Springfield, to 390 Sumner Avenue, Springfield, where he will continue in the practice of proctology.

BOSTON GASTROENTEROLOGICAL SOCIETY

A meeting of the Boston Gastroenterological Society will be held in the Cheever Amphitheater, Boston City Hospital, on Wednesday, January 28, at 8 p.m.

Dr. Thomas P. Almy, assistant professor of medicine, Cornell University Medical College, will speak on the subject

"Modern Concepts of Ulcerative Colitis," and Dr. Leland S. McKittrick, clinical professor of surgery, Harvard Medical School, will speak on the subject "Surgical Aspects of Ulcerative Colitis."

All physicians are cordially invited.

NEW ENGLAND CENTER HOSPITAL HOUSE OFFICERS' ASSOCIATION

The House Officers' Association of New England Center Hospital announces the following programs in its Evening Lecture Series:

Friday, January 30. Some Aspects of Acid Base Regulation. Dr. Robert F. Pitts, professor of physiology and biophysics, Cornell University Medical College (discussers, Drs. Maurice B. Strauss and William B. Schwartz).

Friday, February 20. Some Contributions to the Physiology of Gastric Secretions and the Peptic-Ulcer Problem. Dr. Lester R. Dragstedt, professor of surgery and chairman, Department of Surgery, University of Chicago School of Medicine (discussers, Drs. Reginald H. Smithwick and Charles G. Child).

These programs will be held at 7 p.m., in the Stearns Auditorium of New England Center Hospital. All interested persons are invited to attend.

TUFTS MEDICAL ALUMNI LECTURE

The annual Tufts Medical Alumni Lecture will be given at Tufts College Medical School on Tuesday, February 3, at 11 a.m. Dr. Joseph B. Kirsner (M '33), professor of medicine at the University of Chicago School of Medicine, will speak on the subject "Some Recent Advances in Gastroenterology." Physicians and students are invited to attend.

SELECTIVE SERVICE SYSTEM

The Selective Service System and the Department of Defense have undertaken several programs for completing the call up of physicians in Priority I and Priority II so far as possible before starting the call for Priority III physicians. These actions include re-examination of certain physically disqualified physicians of Priority I and Priority II to determine whether or not they can be qualified by virtue of a waiver on the part of the armed forces of certain conditions so that most physicians who carry on active professional careers in civilian life can be commissioned; and a review of the essentiality of special registrants deferred or reserve officers delayed who are in Priority I and Priority II to determine the present status of their essentiality to the national health, safety or interest or, conversely, their availability for military service.

Advice on the essentiality of these physicians should be strongly supported by evidence of their current essentiality to community, medical school or hospital. Any such advice should be for the shortest time possible and in any case in which it is comtemplated that deferment of either Priority I or Priority II registrants or reservists should be extended beyond June 1, 1953, full information with supporting documentation should be forwarded to the National Advisory Committee for adjudication.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 16–30. Combined Anesthesia Teaching Conferences of Boston. Page 785, issue of November 13.

JANUARY 16–31. Springfield Hospital Educational Program. Page 1000, issue of December 18.

JANUARY 19–APRIL 20. Hartford Medical Society. Page 42, issue of January 1.

JANUARY 20. South End Medical Club. Page 41, issue of January 1.

JANUARY 21. Combined Meeting of Greater Boston Medical and Dental Societies. Page 80, issue of January 8.

JANUARY 21. Boston Graduate Club of Phi Delta Epsilon Medical Fraternity. Page 1050, issue of December 25.

JANUARY 21. New England Society of Physical Medicine. Page 41, issue of January 1.

JANUARY 21–APRIL 8. Postgraduate Medical Institute. Boston. Page 452, issue of September 18.

JANUARY 26–MARCH 23. Postgraduate Course in General Medicine. Cushing Veterans Administration Hospital, Framingham. Page 697, issue of October 30.

JANUARY 28. Lahey Clinic Lectures. Page 1050, issue of December 25.

JANUARY 28. Boston Gastroenterological Society. Page 123.

JANUARY 28–APRIL 1. Postgraduate Medical Institute Course in General Medicine. Burbank Hospital, Fitchburg. Page 1049, issue of December 25.

JANUARY 30. First Public Health Workshop on Dental Care in Industry. Page 41, issue of January 1.

JANUARY 30 AND FEBRUARY 20. New England Center Hospital House Officers' Association. Notice above.

FEBRUARY 3. Tufts Medical Alumni Lecture. Notice above.

FEBRUARY 6. New England Society of Anesthesiologists. Page 827, issue of November 20.

FEBRUARY 6. American College of Radiology. Page 1001, issue of December 18.

FEBRUARY 7–JUNE 2. Mount Auburn Hospital Panel Discussions. Page 868, issue of November 27.

FEBRUARY 9 AND 10. Annual Congress on Medical Education and Licensure. Page 786, issue of November 13.

FEBRUARY 23 AND 24. American College of Surgeons. Page 42, issue of January 1.

MARCH 2–5. New Orleans Graduate Medical Assembly. Page 828, issue of November 20.

MARCH 2–MAY 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

APRIL 3. New England Society of Anesthesiologists. Page 418, issue of September 11.

APRIL 29 AND OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

MAY 19–21. Massachusetts Medical Society. Hotel Statler, Boston.

MAY 25–31. First World Congress on Fertility and Sterility. Page 1001, issue of December 18.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

MAY 13. Andover Country Club, Shawsheen.

MIDDLESEX WEST

JANUARY 26–MARCH 23. Postgraduate Course in General Medicine. Cushing Veterans Administration Hospital, Framingham.

NORFOLK

JANUARY 27.
FEBRUARY 24.
MARCH 24.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 22

THURSDAY, JANUARY 22

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
12:00 m. Consultation Rounds. Cardiovascular. Psychiatry. Boston City Hospital.
*12:00 m.–1:00 p.m. Surgical Therapy of Pulmonary Tuberculosis. Dr. Norman J. Wilson, Jr. Stearns Auditorium, New England Center Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.
*7:30 p.m. Interpretation of Electrocardiograms. Lectures and Demonstration given by Drs. E. E. Hinton, C. C. Bailey and Walter Goodale. New England Deaconess Hospital.

FRIDAY, JANUARY 23

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit. 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Dr. George W. Thorn and Dr. Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
*10:30 a.m.–1:30 p.m. Combined Medical and Surgical Rounds, Stearns Auditorium, New England Center Hospital.
11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*2:00–3:00 p.m. Pulmonary Conference. Drs. Kane, Etsten and others. Stearns Auditorium, New England Center Hospital.
*4:00–6:00 p.m. X-ray Conference. Drs. Sosman and Hare. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.
*7:00–9:00 p.m. Combined Anesthesia Teaching Conferences of Boston. Amphitheater, Evans Memorial, Massachusetts Memorial Hospitals. Eighth Floor, 65 East Newton Street.

SATURDAY, JANUARY 24

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*10:00 a.m. Combined Rounds. Heart Station Conference Room, Boston City Hospital.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

(Notices concluded on page xix)

still winning new friends

right through the menopause

on oral estrogen therapy that imparts

no odor or after-odor, no taste or after-taste

YOUR prudent and assuring explanations will help—clearing away the jungle of her doubts and fears. Then SULESTREX will help—in controlling the physical symptoms of the climacteric.

Years of search have given you SULESTREX—an odorless, absolutely pure, crystalline estrogen, chemically standardized for unvarying hormonal activity. Unexcelled—therapeutically *and* esthetically—these tiny uncoated tablets will never insult the breath or perspiration, never annoy with "after-taste."

A new report by Reich and associates[1] confirms and extends his conclusions from his pilot study[2]...

"Piperazine estrone sulfate* (SULESTREX) *is a clinically effective oral estrogenic substance, easy to administer and extremely well tolerated. Its action is accompanied with an amazingly low incidence of side reactions."

175 patients were included in this latest study, 50 of whom received therapy to relieve postpartum breast engorgement.

Make your own test—on your next menopausal patient. One trial will give impressive argument for this newest advance in oral estrogen therapy. SULESTREX is available in 0.75-, 1.5-, and 3-mg. grooved tablets.

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1. Reich, W. J., et al. (1952), A Recent Advance in Estrogen Therapy. II. Amer. J. Obst. & Gynec., 64:174, July. 2. Reich, W. J., et al. (1951), A Recent Advance in Estrogen Therapy. I. Amer. J. Obst. & Gynec., 62:427, August.

1-81

Sgt. 1st Class Einar H. Ingman U. S. Army Medal of Honor

THE REDS IN AMBUSH on the ridge had lain concealed, withholding their fire. Now they opened up. The two squads were trapped. Their leaders were wounded; others were dropping.

Sergeant Ingman took command. He reorganized the survivors, assigned fields of fire, encouraged the men to fight. A red machine gun opened fire. The sergeant charged it alone, hit it with a grenade.

Then he tackled another gun. A grenade and a burst of fire knocked him down, badly wounded. He got up, reached the gun, and dispatched the entire crew. When his squad reached him, they found Sergeant Ingman unconscious—but 100 of the enemy fleeing in panic.

"Bucking the Communists," says Sergeant Ingman, "takes an awful lot of staying power. The G.I.'s have got it. You have, too, when you invest part of your hard-earned pay *regularly* in U. S. Defense Bonds."

Bonds are first of all a cash saving for you. But they're also back of our country's *production power*. Which couples up with G.I. *fire power* to keep the peace for all.

"The sergeant charged alone . . ."

Peace is for the strong!
For peace and prosperity save with
U.S. Defense Bonds!

Now E Bonds pay 3%! Now, improved Series E Bonds start paying interest after 6 months. And average 3% interest, compounded semi-annually when held to maturity! Also, all *maturing* E Bonds automatically *go on* earning—at the new rate—for 10 *more* years. Today, start investing in Series E Defense Bonds through the Payroll Savings Plan.

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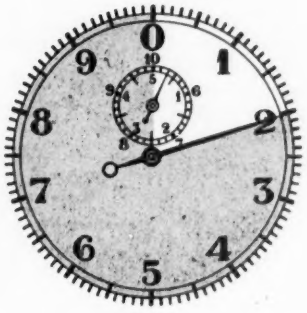
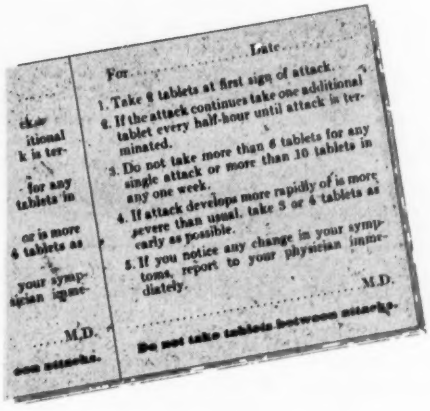


minutes are of the essence in migraine therapy . . .

Pharmacotherapy, psychotherapy, physiotherapy and surgery, may be employed individually or in combination for therapy of head pain. De Jong's concept of pharmacotherapy in migraine may well be employed to treat most cephalalgias; first—treat or shorten the individual attack and second—prevent the recurrence or lengthen the intervals between attacks.

The first principle in treating the headache is to start immediately when the first sign of trouble appears. The earlier treatment is started, the more successful it is likely to be.

De Jong, R. N.: Chicago M. Soc. Bull. *54*:106 (Aug.) 1951.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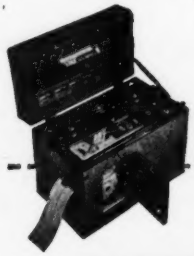

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NOTICES (*Concluded from page 124*)

MONDAY, JANUARY 26

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Hematology Conference. Dr. Dameshek. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, JANUARY 27

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
12:00 m. Consultation Rounds. Infectious Diseases. Gastrointestinal. Boston City Hospital.
*12:00 m.–1:00 p.m. Tumor Clinic. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, JANUARY 28

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Medical Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.
*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Neuropathology Conference. Drs. Adams and MacMahon. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
6:30 p.m. Combined Meeting (and Dinner) of the Greater Boston Medical and Dental Societies. Shelton Hotel.
*7:30 p.m. Lahey Clinic Lectures. Symposium on Rheumatic Heart Disease. Drs. Robert E. Foley, Herbert D. Adams and Ferdinand A. Salzman. Joslin Auditorium, New England Deaconess Hospital.
8:00 p.m. Boston Gastroenterological Society. Cheever Amphitheater, Boston City Hospital.

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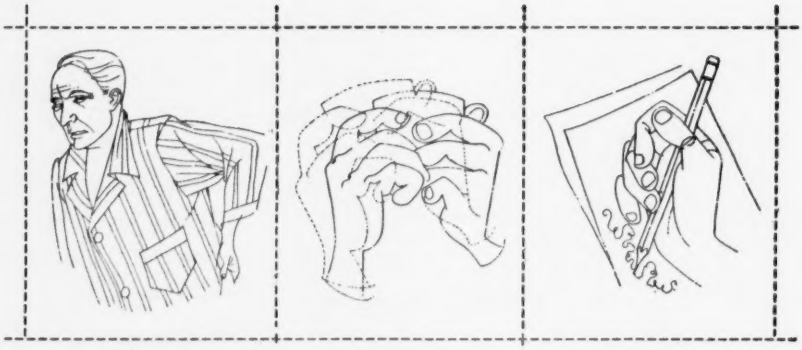

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